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Synthetic Approaches to TAT

Final Technical Report

by

HEINRICH WAMHOFF, MARCUS BONGEN, AND JOHANNES NAGELSCHMITZ

DECEMBER 1988

United States Army

EUROPEAN RESEARCH OFFICE OF THE U.S. ARMY

London, England

CONTRACT NUMBER DAJA 45-85-C-0016

Professor Dr. Heinrich Wamhoff, Contractor

Approved for Public Release; distribution unlimited

Unclassified
SECURITY CLASSIFICATION OF THIS PAGE

A205 451

REPORT DOCUMENTATION PAGE

1a. REPORT SECURITY CLASSIFICATION Unclassified	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT Approved for public release; distribution unlimited
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S) R&D 4480-CH-01
6a. NAME OF PERFORMING ORGANIZATION Institut für Organische Chemie und Biochemie 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION USARDSG(UK)
6c. ADDRESS (City, State, and ZIP Code) Universität Bonn, Gerhard-Domagk-Str. 1 D-5300 Bonn 1, Federal Republic of Germany	7b. ADDRESS (City, State, and ZIP Code) Box 65 FPO New York 09510-1500
8a. NAME OF FUNDING/SPONSORING ORGANIZATION USARDSG(UK) 8b. OFFICE SYMBOL (If applicable) AMXSN-UK-RC	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER DAJA45-85-C-0016
8c. ADDRESS (City, State, and ZIP Code) Box 65 FPO New York 09510-1500	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. 61103A; PROJECT NO. 1L161103BH57; TASK NO. 08; WORK UNIT ACCESSION NO. DA312140

11. TITLE (Include Security Classification)

(U) New Synthetic Approaches to TAT

12. PERSONAL AUTHOR(S)
Prof. Heinrich Wamhoff, Dr. Marcus Bongen, Dr. Johannes Nagelschmitz

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Final	FROM 1985 TO 1988	1988, December, 5	39

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	
07	03		Synthetic approaches; 1,3,5,7-tetrazocanes; Octahydro-1,3,5,7-tetrazocines; TAT; Urotropine; Hexamethylenetetramine; DAPT; Degradation; Total syntheses; CONTINUED

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

This Final Technical Report describes some approaches to 1,3,5,7-tetraacetyl-octahydro-1,3,5,7-tetrazocine "TAT". The development of novel and simple TAT syntheses of easily accessible starting materials belongs to the very basic and substantial requirements in the field of TAT and HMX research. Therefore this project belongs to the leading and very important desires of the Synthesis Section of ARDEC, Dover, NJ (E.E. Gilbert, private communication).
In pursuing this project, the following strategies have been developed and checked experimentally:
(1) Degradation experiments of urotropine (hexamethylenetetramine) and 3,7-diacetyl-1,3,5,7-tetraazabicyclo[3.3.1]nonane (DAPT).
(2) Approaches to total syntheses of tetrazocanes according to the general scheme:
2 C-N-C + 2 N-R and 2 N-C-N + 2 O=C.

CONTINUED

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION	
☒ UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT. ☐ DTIC USERS	Unclassified	
22a. NAME OF RESPONSIBLE INDIVIDUAL Dr. Robert J. Campbell	22b. TELEPHONE (Include Area Code) 01-409 4423	22c. OFFICE SYMBOL AMXSN-UK-RC

DD FORM 1473, 84 MAR — 83 APR edition may be used until exhausted. All other editions are obsolete.

SECURITY CLASSIFICATION OF THIS PAGE
Unclassified

Block 18 continued.

Cyclic ureides; Glykoluriles; Tetramerization of methyleneimines; Tetrazocane-Co^{2+} complexes; Stability requirements; Resonance stabilization; Internal; External stabilization; X-ray analysis; Structure and reactivity; Synthetic requirements.

Block 19 continued.

(3) Synthetic approaches to cyclic ureides starting from ureas and reduction experiments.
(4) On the chance of making tetrazocines via glykoluriles.
(5) On the tetramerization of methyleneimines.

As has been found in the course of this project, the route leading to stable tetrazocanes is a rather small and narrow ridge pathway which reduces the preparative approaches dramatically to very few procedures, where resonance stabilized tetrazocanes externally substituted e.g. by N-acetyl or N-nitro groups or, internally, by amidic ring carbonyl groups are finally formed.
In all other cases, decomposition of the building units or of the primary formed heterocycles takes rapidly place either into 6-membered 1,3,5-triazine derivatives or polymeric materials, the latter almost not to characterize. As a consequence, some rules have been set up for advantageous TAT syntheses.
In the course of this research work, besides a plenty of not successful experiments, a novel modification of TAT synthesis has been worked out starting from DAPT as well as from MBA and formaldehyde. Furthermore, a more detailed preparation procedure of a Roumanian approach to a Co^{2+} -complex of 1,3,5,7-tetraphenyl-1,3,5,7-tetrazocane has been developed.

1. Summary

This Final Technical Report describes some approaches to 1,3,5,7-tetraacetyl-octahydro-1,3,5,7-tetrazocine "TAT". The development of novel and simple TAT syntheses of easily accessible starting materials belongs to the very basic and substantial requirements in the field of TAT and HMX research. Therefore this project belongs to the leading and very important desires of the Synthesis Section of ARDC, Dover, NJ (E.E. Gilbert, private communication).

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In the course of this research work, besides a plenty of not successful experiments, a novel modification of TAT synthesis has been worked out starting from DAPT as well as from MBA and formaldehyde. Furthermore, a more detailed preparation procedure of a Roumanian approach to a Co^{2+}-complex of 1,3,5,7-tetraphenyl-1,3,5,7-tetrazocane has been developed.

2. List of Key-Words

Synthetic approaches, 1,3,5,7-tetrazocanes, octahydro-1,3,5,7-

tetrazocines, TAT, urotropine, hexamethylenetetramine, DAPT, degradation, total syntheses, cyclic ureides, glykoluriles, tetramerization of methyleneimines, tetrazocane-Co^{2+} complexes, stability requirements, resonance stabilization, internal, external stabilization, X-ray analysis, structure and reactivity, synthetic requirements.

3. Table of Contents

page

4. List of Appendixes

(d) General Procedure for the Reaction of DAPT with Organic Halides

(e) Reaction of Methylenebisacetamide (MBA) with Formaldehyde

(f) Synthesis of Cyclic Ureides according to Kadowaki[22a)]

(g) Reduction of the Bisureides with $Na(Li)BH_4$/ THF/TMSCl

(h) Synthesis of t-Butylmethyleneimine

(i) Synthesis of the "Green Complex" following the Roumanian Approach

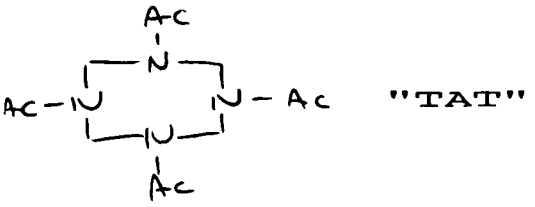
(k) Publications from this Contract

(l) List of Participating Scientific Personnel

5. Report (Body of Report)

5.1 Introduction

The purpose of this research project was to develop novel synthetic approaches to 1,3,5,7-tetraacetyl-1,3,5,7-octahydrotetrazocine abbreviated "TAT" [1)]



"TAT"

This tetraacetylated derivative of a [8]ane-N_4 compound represents one of the few stable and isolable derivatives of this type. Its crystal structure has been determined[2)]:

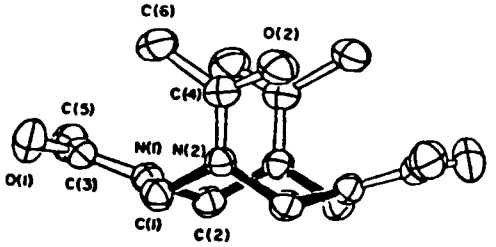
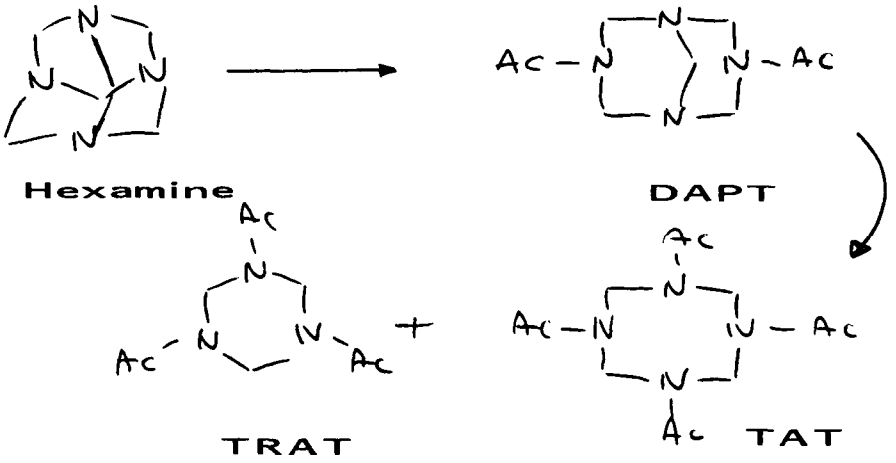


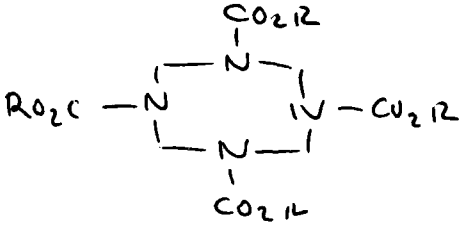
Fig. 1

TAT is an important intermediate for HMX, 1,3,5,7-tetranitro-1,3,5,7-octahydrotetrazocine, a most powerful military explosive. But the syntheses known hitherto are much more expensive than for preparing RDX[3].

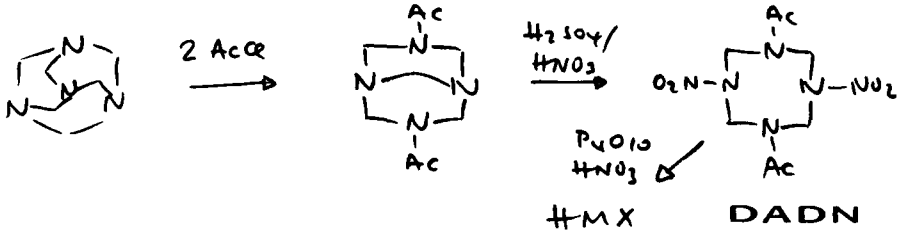
In the meantime, alternative procedures have been reported starting with urotropine[4] and DAPT[1] (3,7-diacetyl-1,3,5,7-tetraazabicyclo[3.3.1]nonane[5]. The protonation equilibria and degradation reactions of hexamine in aqueous HCl forming DAPT, TAT and TRAT has been also reported[6].



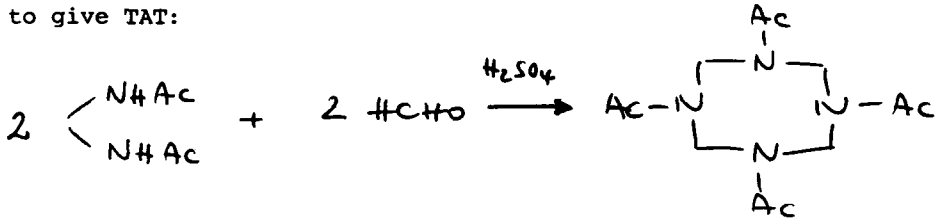
The condensation of urethanes with formaldehyde forming 1,3,5,7-tetracarbalkoxy-1,3,5,7-octahydrotetrazocines in 45% yield is known[7]:



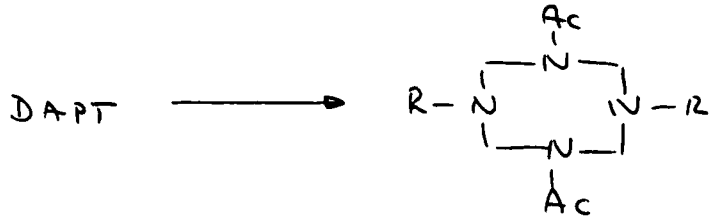
Urotropine reacts in the presence of acetyl chloride to afford DAPT which proved to be a versatile educt for further reactions[5,8,9].



Another TAT approach was described by Coon[10]; methylenebisacetamide (MBA) reacts with paraformaldehyde under anhydrous conditions to give TAT:



Russian authors claim another tetrazocine approach by reacting DAPT with benzyl chloride or propargyl bromide[11]:



5.2 Degradation of Urotropine and DAPT

In order to develop alternative methods for the preparation of TAT and related derivatives with regard to urotropine and DAPT, several potential novel approaches have been designed and proved experimentally:

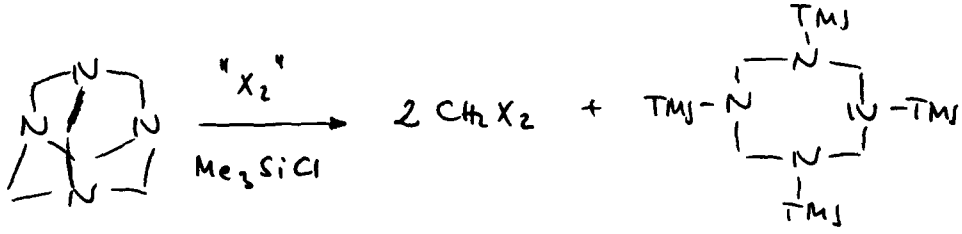
* degradation of hexamine (urotropine)
* degradation of DAPT

With regard to Urotropine many C-N cleavage experiments have been carried out employing various reagents, cf. Table 1.

Table 1. Selection of some degradation experiments on urotropine

Reagent	Solvent	Temperature	Result
acetyl chloride	neat	50°C	starting material
Cl_2PPh_3/TMSCl	CH_2Cl_2	38°C	decomposition
$POCl_3$/TMSCl	"	"	starting material & decomposition products
Br_2PPh_3/TMSCl	"	"	" "
TMSCl (autoclav)	neat	60-70°C	decomposition products

General Scheme:



As can be seen from the results, the partial destruction of urotropine looks like a walk on a small ridge: either the conditions are too mild and the starting material is recovered, or the conditions are too drastic, and only decomposition products are the result; sometimes a mixture of unchanged urotropine and non-identificable break down products have been obtained.

Also electrochemical cleavage experiments have been carried out on the urotropine molecule. The determination of the oxidation potential has been made by cyclic voltametry.

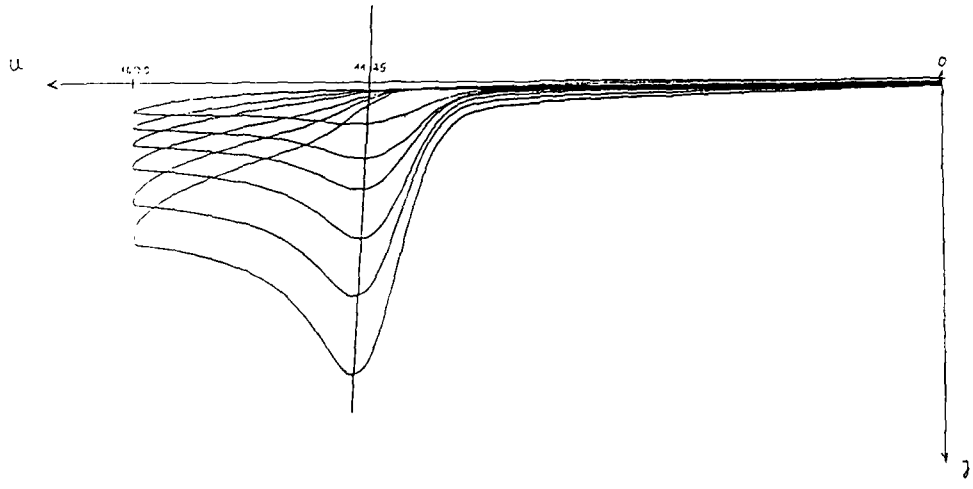


Figure 2. Cyclic voltagram of urotropine

The first electrochemical measurements in MeCN have been reported by Nelson and Hintz[12]; MeOH was choosen as solvent for our measurements. From the diagram follows that the electrochemical oxidation of urotropine is irreversible; only oxidation and no reduction peaks are observed. Most obviously, a rapid reaction

with the solvent seems to take place. The oxidation potential has been determined to

1125 mV , vs. $Ag/AgNO_3$ reference electrode

i.e. 1695 mV vs. normal H_2-electrode

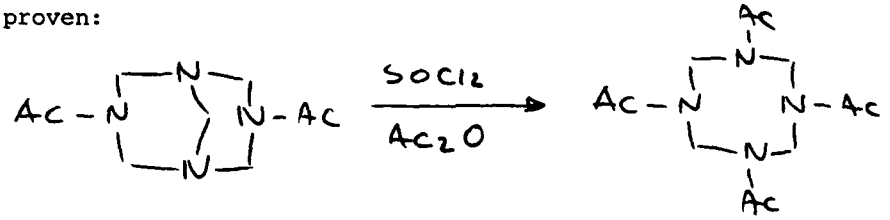
Galvanostatic conditions (constant current) werde choosen working in a 40 ml-Metrohm cell with a solution of 0.2 g urotropine in 20 ml MeOH with 0.2 mol $LiClO_4$ as electrolyte;

U = 14....18 V; I = 100 mA; T = 35°C; Anode: glassy carbon cylider; Cathode: Pt-wire.

Working up the product mixture formed during the electrolysis (column chromatography on silicagel; solvent: $CHCl_3$) did not yield any isolable component; thus, total decomposition has occured during the electrolysis.

Furthermore, many DAPT degradation experiments have been carried out, as this molecule needs only one methylene bridge to be splitted off, and carries already two stabilizing acetyl groups. The Table 2, page -10- informs about the conditions choosen and the results obtained.

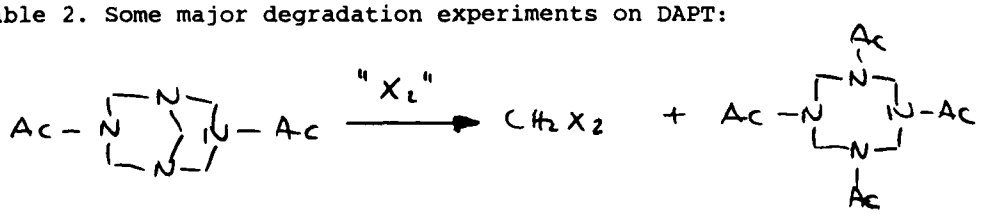
These experiments show once again the ridge walk character of these degradation experiments on DAPT. But at least, in one case a novel and easy access to TAT has been experimentally proven:



DAPT is added to a mixture of $SOCl_2$, NH_4OAc, and traces of water in acetanhydride. The mixture warms up, and after returning to room temperature all volatile material is evaporated. The TAT obtained from this reaction is recrystallized from ethanol; yield: 53%.

From these degradation experiments follows that C-N cleavage of the bridges in urotropine and DAPT need a ceratin energy which is either not reached or overstepped. In case that tetrazo=

Table 2. Some major degradation experiments on DAPT:



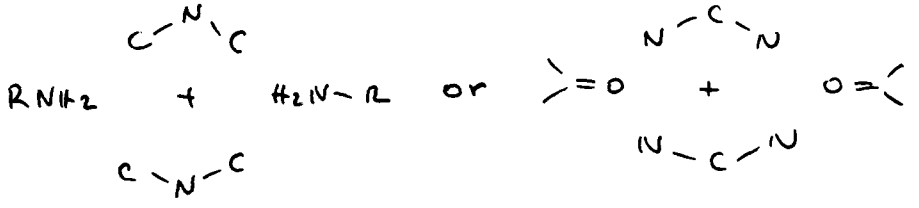
Reagent	Solvent	Temperature	Result
Cl_2PPh_3/TMSCl	CH_2Cl_2	38°C	decomposition
AcCl	neat	50°C	starting material
pTsA/$AlCl_3$	ethyl acetate acetanhydride	1)r.t. 2)70°C	starting material
$ClSO_3H$/$AlCl_3$	CH_2Cl_2	1)r.t. 2)38°C	starting material
t-BuCl/$AlCl_3$	ligroin/CH_2Cl_2 or t-BuCl	1)r.t. 2) 38°C	starting material
NBS	CCl_4	70°C	starting material
NaOCl	-	0°C	starting material
pTSA	-	50°C	starting material
$SOCl_2$/Ac_2O	Ac_2O	1)0°C 2)r.t.	TAT
TMSCl/$AlCl_3$	TMSCl	1)r.t. 2)refl.	starting material
$AlCl_3$/CH_2Cl_2	CH_2Cl_2	1)r.t. 2)38°C	starting material
PCl_5	Ac_2O	100°C	starting material + decomposition prod.
$COCl_2$	toluene	80°C	starting material + decomposition prod.

cine degradation products are formed, these are decomposing in situ, except they are at once intercepted by stabilizing groups, such as acetyl or nitro groups. TMS and alkyl groups seem to be not sufficient stabilizing, except the Russian claim with bulky substituents[11].

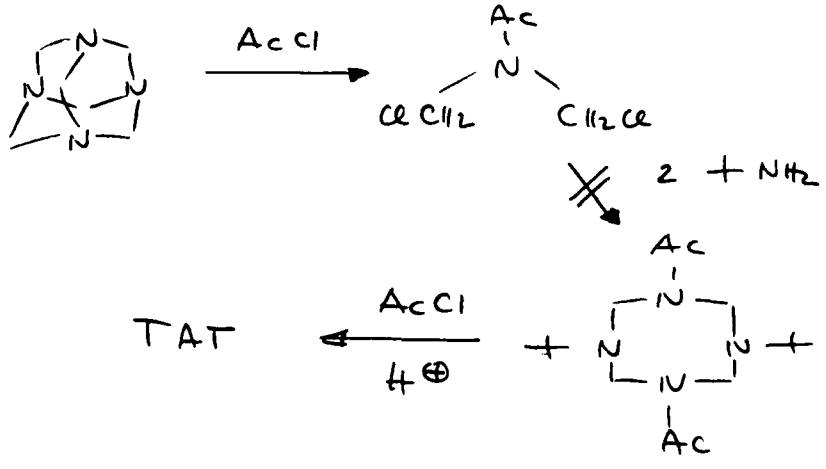
5.3 Approaches to Total Syntheses of Tetrazocines

While the synthesis of 5- and 6-membered carbocyclic and heterocyclic rings does not meet with greater problems, the approach to medium sized rings offers lot of difficulties, as polymerization reactions compete always with the current cyclization reactions, whcih can be normally avoided, e.g. by applicatrion of the Ruggli-Ziegler high dilution principle[13] or in case of macrolide synthesis by employing modern carbonyl activating reagents as developed by Mukaiyama[14] and Corey[15], or with the aid of template effect[16].

In this course, we have started from three-atomic increments -C-N-C- or -N-C-N- in the following general scheme:

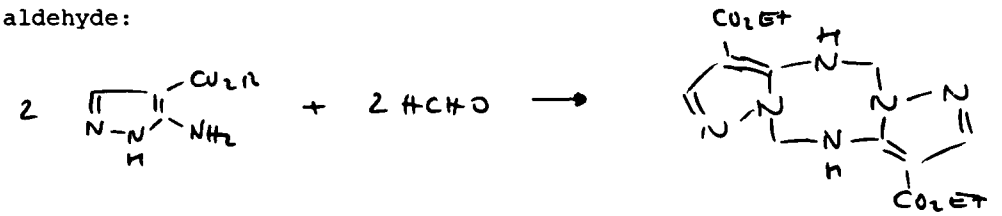


One typical reactant with a C-N-C sequence is N,N-bis-chloromethyl-acetamide easily accessible from urotropine degradation[17]:



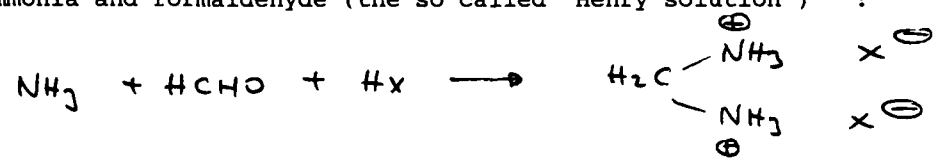
In this sense, two equivalents of t-Bu-amine should lead to a tetrazocine, a TAT precursor, convertible to TAT by replacement of the t-Bu groups. In several attempts, however, only traces of an oily mixture have been obtained, which could be not separated by column or thick layer chromatography.

Another promising approach using N-C-N-increments for building up a heterocondensed tetrazocine has been found by our group[18], starting from easy accessible pyrazole enamino esters and formaldehyde:

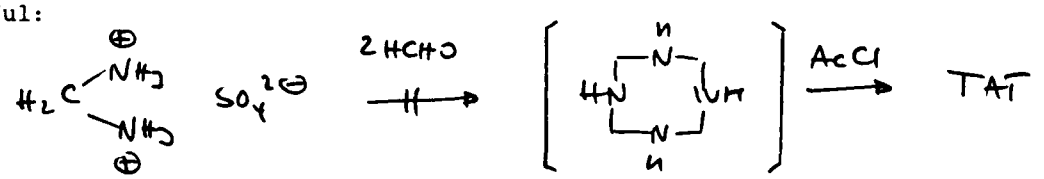


In this case the tetrazocine ring is stabilized by both condensed pyrazole rings leading to a kind of vinylogeous cyclic ureide structural type. Break-down attempts of this tricycle under strong acetylating conditions will be one topic of the just starting following contract No. DAJA 45-89-C-0003.

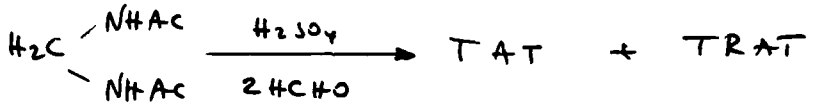
Unsubstituted methylene diamines are formed from a mixture of ammonia and formaldehyde (the so called "Henry solution")[19]:



On trying to condense the methylenediamine disulfate with formaldehyde under basic condistions to obtain a perhydrotetrazocine, interceptable by acetylation to TAT, was, however, not successful:



As Coon[10] has claimed in a Patent, TAT is formed besides 1,3,5-triacetyl-hexahydro-1.3.5-triazine (TRAT) by reacting methylenebisamide (MBA) with formaldehyde:



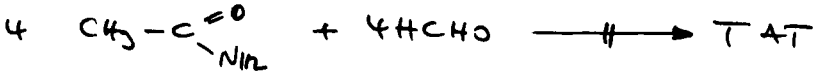
TAT is, however, obtained in only 17% yield, so that an improvement seemed to be desirable. MBA is easily accessible from acetamide and formaldehyde[20].

In our experiments, MBA was warmed with paraformaldehyde and some drops H_2SO_4 in aqueous solution. With the aid of t.l.c. we have been able to detect traces of TAT. No reaction was observed when MBA was allowed to stay with aq. HCHO, as well as mixtures of MBA, paraformaldehyde and p-TSA in CCl_4.

Also experiments of MBA and paraformaldehyde in cc. H_2SO_4 turned out to be not successful. In cold cc H_2SO_4 MBA was receovered unchanged while heating of the reaction mixture lead to total decomposition.

The addition of Caesium acetate in a buffered system, a powerful catalyst in condensation and cyclization experiments[21] did not show any effect. Employing CsOH in equivalent quantities, however, lead to decomposition of the reaction mixture (NH_3 evolution).

We have also tried in a "one pot" reaction to condense directly acetamide and paraformaldehyde in the presence of CsAc:



But no TAT was detectable.

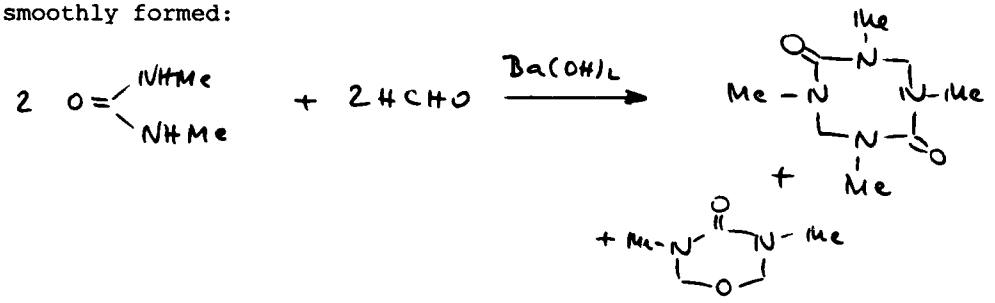
Similarly, methylenebisacetamide after deprotonation with NaH did not show any reaction with methylene iodide.

As a consequence of these results, one can conclude that obviously the basicity of both acetylated N-atoms is too weak for performing nucleophilic attacks to the formaldehyde carbonyl group.

5.4 Synthetic Approaches to TAT Starting from Ureas

Ureas are versatile starting materials for the generation of heterocycles, as show the classical condensations to give e.g. barbiturates or quinazolines.

Kadowaki[22] has firstly employed N,N'-dimethylurea from a tetrazocine synthesis. With formaldehyde the stable cyclic ureide is smoothly formed:



1,3,5,7-Tetramethyl-1,3,5,7-perhydrotetrazocine-2,6-dione is obtained in 13% yield besides 3,5-dimethyl-1,3,5-tetrahydrooxadiazin-4-one, obviously a degradation product of the tetrazocane.

This work could be nicely reproduced. One reason for the stability of this cyclic ureide is once again the partial amide structure of this molecule and its amide resonance. Very recently, the structure of this cyclic ureide has been unambigously established by single crystal X-ray analysis[23]:

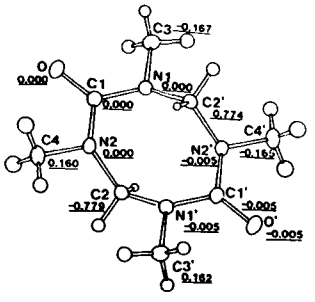
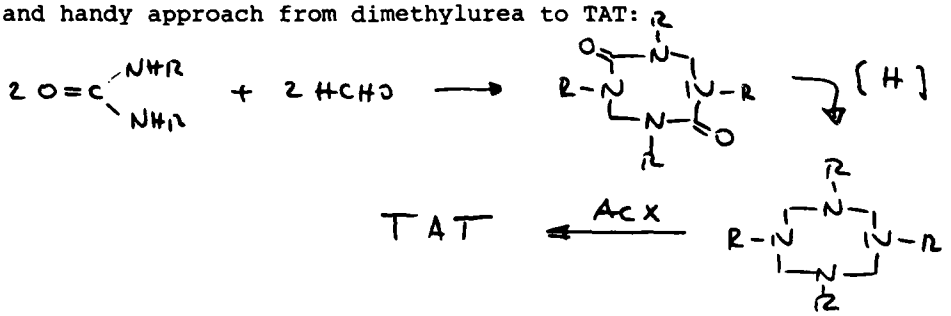


Figure 3. The structure of 1,3,5,7-tetramethyltetrahydro-1,3,5,7-tetrazocine-2,6(1H,3H)-dione projected on the plane composed of O, C_1, and N_2.

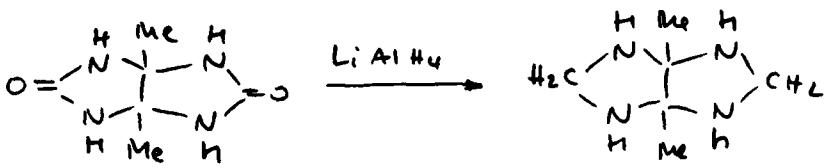
The ORTEP plot shows this molecule accordingly in a planar conformation (in contrast to TAT, which possesses a crown type conformation).

Basing upon these results and the easy accessibility of the cyclic ureides, we planned to convert these ureides by reductive methods into the tetrazocines and to exchange the alkyl substituents for acetyl groups resulting into TAT; this would be a nice and handy approach from dimethylurea to TAT:

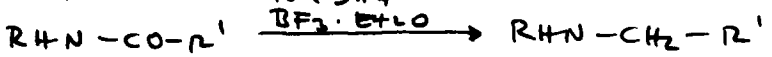


However, the first disappointing fact we found, was that this cyclocondensation reaction could not be transferred to any other dialkylurea, except dimethylurea. Perhaps, steric effects play a decisive role in this cyclization step.

Then we tried in a model experiment to reduce the cyclic ureide to a tetrazocine. Normally cyclic ureas can be easily reduced with the aid of $LiAlH_4$[24], as e.g.



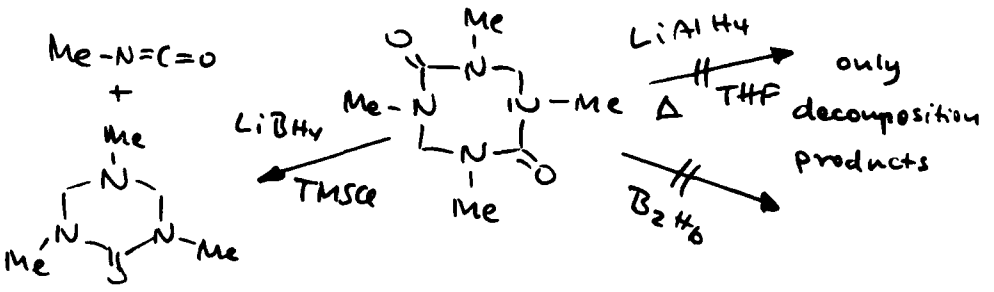
Another procedure consists of treatment of amides with $NaBH_4/BF_3$-etherate/THF[25]:



Secondary amides are successfulle reduced with the couple borane-dimethylsulfide in the presence of BF_3-etherate[26].

On reacting the cyclic ureide with $LiAlH_4$ in refluxing THF under Argon only decomposition products of the starting material could be found by t.l.c. accompanied by a typical amine smell.

However, the same procedure carried out at room temperature gave only again back the starting material:



With diborane, produced in situ from $NaBH_4$ and BF_3-etherate[27] starting first at 0°C and warming up to the boiling point of THF, again a plenty of decemposition products could be shown by t.l.c.. All separation and isolation procedures were unsuccessful.

Then, we turned to a rather novel method of selective reduction of carbonyl moieties, developed in our Institute by Giannis and Sandhoff[28]: thereby, $NaBH_4$ or $LiBH_4$ and TMSCl represent a powerful reduction couple, which is capable of easy reductions of amino acids, vinylogeous cyanides under comparatively mild conditions. So far, the exact mechanism is still under consideration; first hypothesis is, as follows:

$$LiBH_4 + Me_3SiCl \longrightarrow Me_3Si^{\oplus}\,BH_4^{\ominus} + LiCl$$

The Lewis acid Me_3Si^+ formed seems to attack and to polarize the functional group to be reduced:

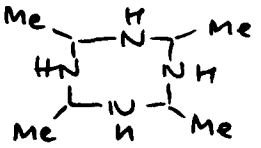
$$R-\overset{\delta+}{C}\equiv\overset{\delta-}{N}\cdots\cdots\overset{\oplus}{Si}Me_3 \xrightarrow{BH_4^{\ominus}} R-CH_2-NH_2$$

Employing $LiBH_4$ as reducing agent, the reduction mixture was stirred for 1 h, in case of $NaBH_4$, the solution was smoothly warmed up. After working up, removal of TMSCl resulted only in traces of a compound which did not show any C=O band in the IR spectrum.

In another experiment, the resulting solution was evaporated. in a small capillary tube and the residue transferred to Mass Spectrometry. From the parent peak m/z 143 follows that after loss of MeNCO 1,3,5-trimethyl-hexahydro-1,3,5-triazin-2-one has been formed, the latter transformation being a known reac-

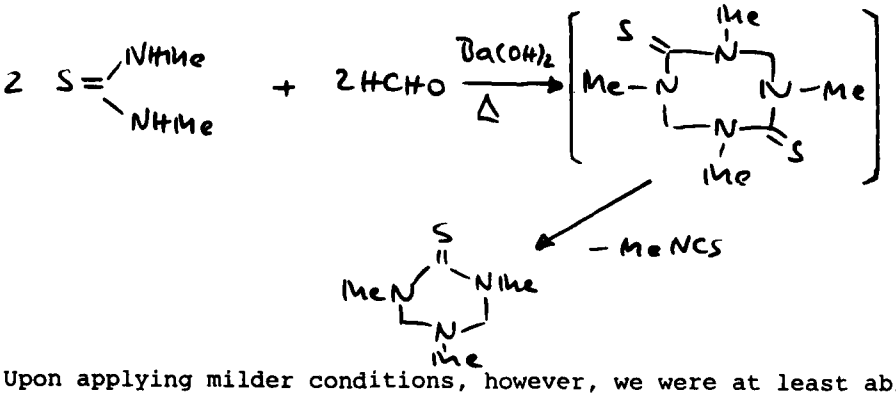
tion[22b]. Thus, also with this powerful reduction agent no definite products could be isolated.

Perhaps, the lack of sufficient stabilizing substituents destabilizes the 8-membered tetrazocine ring, and as a matter of fact, an unsubstituted tetrazocine molecule is not yet known. However, Japanese authors claim that in a gasphase reaction of acetaldehyde and ammonia 2,4,6,8-tetramethyl-1,3,5,7-octahydrotetrazocine is formed[29]:

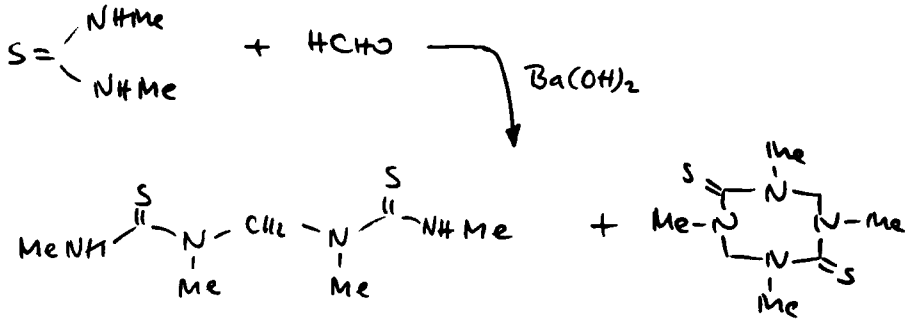


Our experiments, to get acetaldehyde and N,N'-diemthylurea and dimethylurea to reaction was, however, not successful.

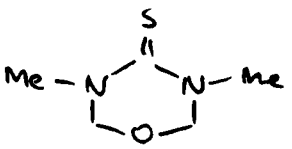
Now, we tried to transfer this cyclic ureide synthesis to thiourea, as we expected that the thioxy group might be reduced under somewhat milder conditions[30]. Thus, we tried the Kadowaki conditions[22]: thiourea, formaldehyde, $Ba(OH)_2$ at higher temperatures. But we obtained, surprisingly, not the expected tetrazocine-dithione, but instead 1,3,5-trimethyl-1,3,5-tetrahydrotriazine-2-thione, obviously by extrusion of methylisocyanate from the 8-membered ring with simultaneous ring contraction:



Upon applying milder conditions, however, we were at least able to detect with Mass Spectrometry that besides an open chain 2:1 adduct also traces of the desired tetrazocine-dithione had been formed:



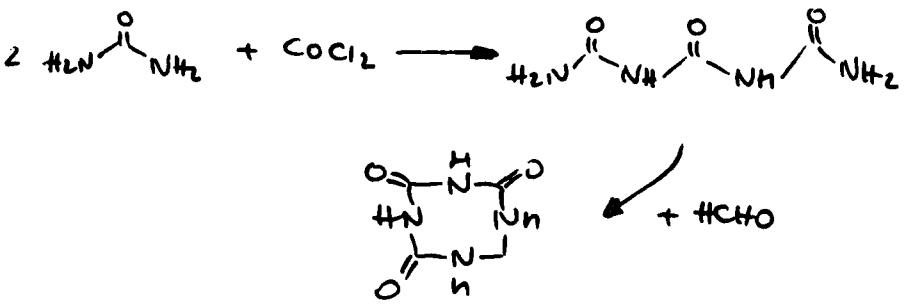
Another experiment in methylenechloride employing paraformaldehyde and p-toluolsulfonic acid as catalyst as well as a separator gave only 3,5-dimethyltetrahydro-1,3,5-oxadiazin-4-thione[31]:



Due to the rather high temperatures required, a thionation of the cyclic ureides according to the method of Lozac'h (P_4S_{10}/ boiling xylene), was not successful.

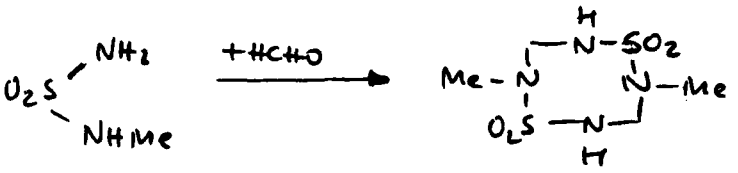
These first preliminary but promising results has induced us to transpone more selective syntheses of this type and subsequent steps into the novel Contract (DAJA 45-89-C-0003 - R&D # 4480A -CH-01).

Furthermore, there are some more promising looking open chain precursors which need just a one-carbon cyclization unit to afford a tetrazocine nucleus. Thus, urea and phosgene furnish a "dimeric" carbonyl-bisurea[32]. This was expected to give in turn with one equivalent formaldehyde a tetrazocine-trione:



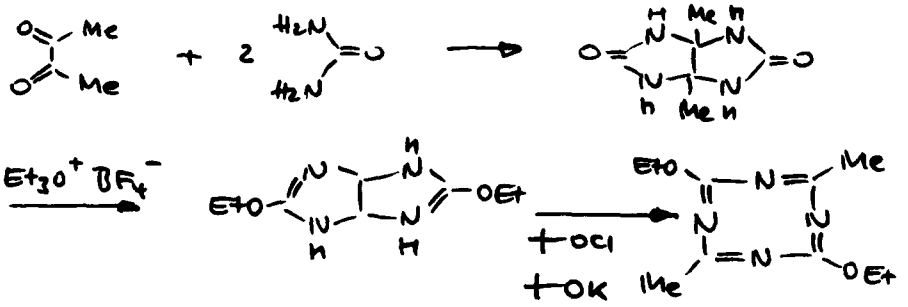
However, treatment with paraformaldehyde in trifluoracetic acid (TFA; solubility !) gave only a polymeric foil-kind product, while formaldehyde affords a complex mixture of decomposition and polymeric products.

Similarly, the known cyclization of monomethylsulfamide with paraformaldehyde in TFA to dithiatetrazocine-tetroxide[33] could not be transferred to urea:



5.5 1,3,5,7-Tetrazocines via Glykoluriles

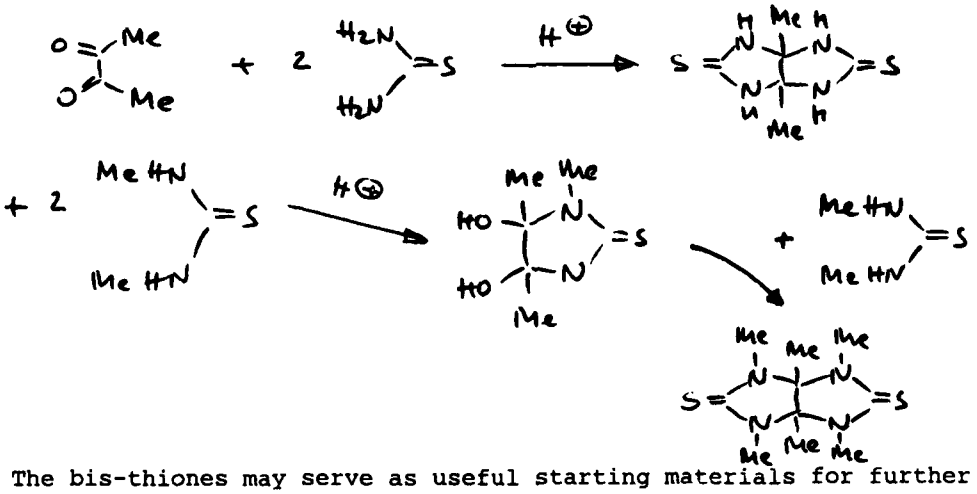
Recently, Gompper and Schwarzensteiner[34] have presented a novel approach, however, to the mostly unsaturated 1,3,5,7-tetrazocines. The first step is a simple 2:1-cyclization of diacetyl and urea to give 1,5-dimethylglykolurile; O-alkylation with $Et_3O^+ BF_4^-$ affords the bis-O-lactimether which is finally converted by t-BuOCl and t-BuOK to a diethoxy-dimethyl-1,3,5,7-tetrazocine:



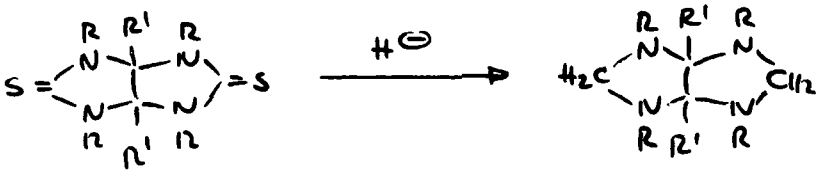
This reaction sequence could be nicely reproduced, but due to our meanwhile experience with the stability of unsubstituted and unstabilized tetrazocines, we doubt if this Gompper approach represents a promising way to obtain at least perhydrotetrazocines.

The transfer of this reaction to other 1,2-diketones, such as cyclohexane-1,2-dione, benzil, oxalic ester etc. could, however, not be realized. But instead, thiourea and dimethylthiourea

afforded with diacetyl the expected dithioxodimethylglykolurils:

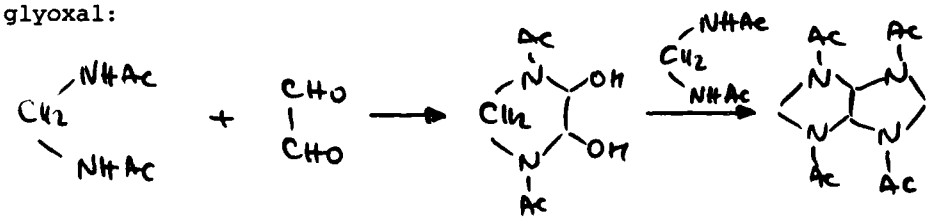


The bis-thiones may serve as useful starting materials for further conversion or cleavage reactions. In addition, complementary reduction experiments with $LiAlH_4$ are currently carried out:

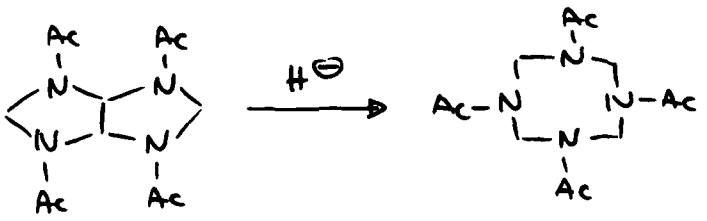


R = H, Me; R' = H, Me

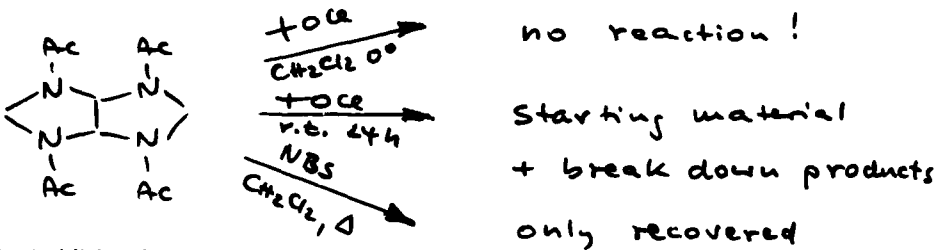
In another study directed to the synthesis of interesting TAT-analogs[35], which appeared while this research project was going on, furthermore, a similar tetraacetylated imidazolo[4,5-b]imidazole was obtained from N,N'.methylenebisacetamide (MBA) and glyoxal:



The crystal structure was established by X-ray analysis. By comparison with TAT, this bicyclic compound is a close relative to TAT, the only difference being a C-C linkage; after C-C cleavage a novel approach to TAT could be possible:



Currently, several oxidative and radicalic orientating ring enlargement experiments have been carried out, so far without any positive result:

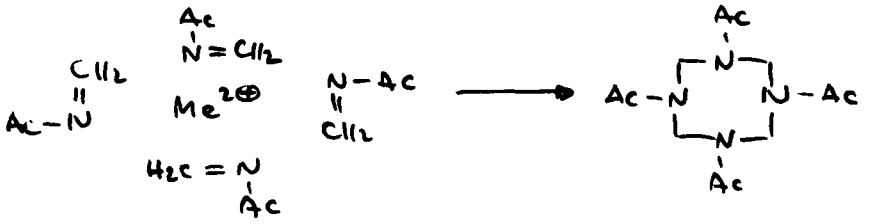


*) cf. "additional remark" p. 39

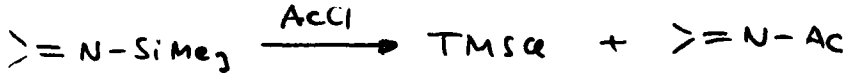
5.6 On the Tetramerization of Imines towards TAT-Synthesis

Another promising approach to TAT synthesis are cyclomerization reactions of suitable methyleneimines with and without the aid of template effect by transition metal catalysis.

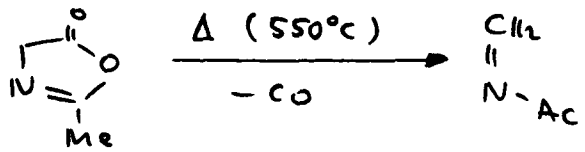
The general scheme of this anticipated approach is shown in the following scheme:



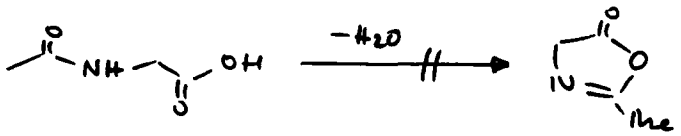
In order to check this potential tetramerization reaction, we had first to look for a suitable generation method for n-acetyl-methyleneimine. This rather unstable building unit can be made on a complicated way from silylated precursors by acetylation[36]:



But even the first stage to deprotonate hexamethyldisilazane with n-BuLi and to obtain silylated methyleneimine by treatment with formaldehyde failed. Therefore, we wanted to get this compound in situ from 2-methyl-5(4H)-oxazolone:

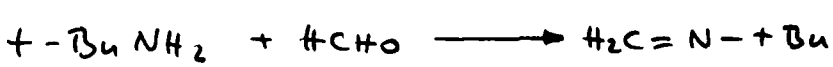


But unfortunately, the experiments to obtain even this cyclized acetylglycine in preparative quantities for further pyrolysis, turned out to be not successful. Thus, in several experiments aceturic acid did not undergo cyclization:



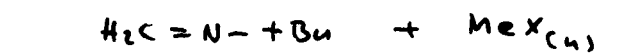
treating it with dicyclohexylcarbodiimide (DCC) under various conditions: r.t., refluxing acetonitrile, excess DCC, addition of NEt_3.

As a consequence of the rather difficult availability of this primary starting material, it was decided to turn to more stable methyleneimines with N-phenyl and N-t-butyl groups. The reaction of t-butylamine with formaldehyde[37] was choosen for further investigations; after some modifications a medium yield of the stable methyleneimine was obtained:



The methyleneimine, however, turned out to be very sensitive against moisture. Then, this methyleneimine was reacted under various conditions with transition metal ions in order to prove its tetramerization tendency under various conditions, employing Zn^{++}, Cd^{++}, and Co^{++} as potential template cations, cf. Table 3, page -23-.

Table 3. Selection of Some Cyclomerization Experiments of t-Butylmethylenimine with Transition Metal Catalysis

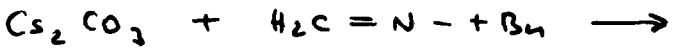


$MeX_{(n)}$	Solvent, Temp.	Products/Results/Remarks
$ZnCl_2$	ether, r.t.	destruction of the imine
$ZnCl_2$	ether, -5°C	no reaction, as salt not soluble
$ZnCl_2$	ether, 30°C	destruction of the educt
$ZnCl_2$	neat, r.t.	vigorous reaction & polymerization
$CdCl_2$	ether, r.t.	no reaction; after some time decomposition
$CdCl_2$	ether, 30°C	destruction
$CoCl_2$	ether, r.t.	no reaction; salt not soluble
$CoCl_2$	DMF, 160°C*	polymerization
$CoCl_2$	DMF, paraformald. t-$BuNH_2$ in situ 2d 120°C	cryst.-amorph. substance mixture crystallization experiments not successful
$CoCl_2$	DMF + HCHO/DMF + t-$BuNH_2$ r.t.	no reaction
"	" 6h-4d 60-120°C	polymerization and destruction

* "Roumanian conditions" [38]

Repeating these reactions many times did not give any definite product which could be analyzed or spectroscopically investigated. Aslo from the polymers we were not able to extract or crystallize any pure compounds.

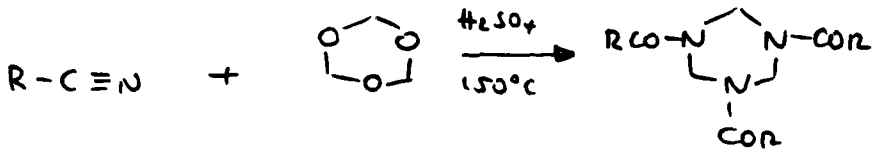
Furthermore, the Cs^+-effect[21] was investigated on this desired tetramerization reaction, and the following experiments have been carried out:



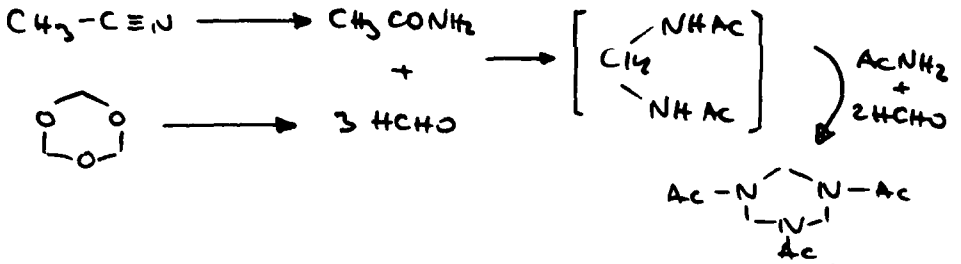
1) r.t. / ether : isolation of the educts
2) 40-50°C, 6h / MeCN: decomposition
3) 80°C, 12 h / MeCN: polymerization

5.7 On the Reaction of Formaldehyde with Nitriles

Some time ago, Gradsten and Pollock have published a study on the reaction of formaldehyde precursors and nitriles[38]. In the presence of catalytic amounts of cc. sulfuric acid, formaldehyde and nitriles have been converted into hexahydro-1,3,5-triazines:



Most obviously, the reaction mechanism can be formulated via methylenebisacetamide (MBA), which cyclizes with a third equivalent nitrile + 2 formaldehyde molecules to afford the triazines shown on the acetonitrile example:



Now, we have got interested if this reaction which most obviously has very similar intermediates in comparison to the foremen-tioned cyclization experiments of MBA could be influenced by the addition of transition metal ions. The results obtained are summarized in the following Table 4 (page -25-).

From these results follows that sometimes the formation of the postulated MBA as an intermediate can be confirmed, but any catalysis of Co^{2+} to afford finally TAT has not been detected. Also the addition of Cs_2CO_3 did not alterate the course of this reaction and the chemical behaviour of the reactants.

Table 4. Reactions of Trioxane and Acetonitrile in the Presence of $CoCl_2$ and $Co(Ac)_2$

Metal Salt	Solvent, Temp., Time	Results/Remarks
$CoCl_2$	DMF/H^+/140°C/1-6 d	degradation products
$CoCl_2$	trioxane soln. 1) r.t. 2) 120-140°C 4h-2d / 6d	MBA
$CoCl_2$	MeCN + 1,3,5-triacetyl-triazine r.t.	no reaction
	" " 1) r.t. 2) 140°C	no reaction
	" " addn. to refluxing solution	decomposition
$Co(Ac)_2$	MeCN, trioxane, CH_2Cl_2 H^+, r.t.	MBA
	" " 80°C	MBA
	" " 120°C, DMF 36 h	decomposition

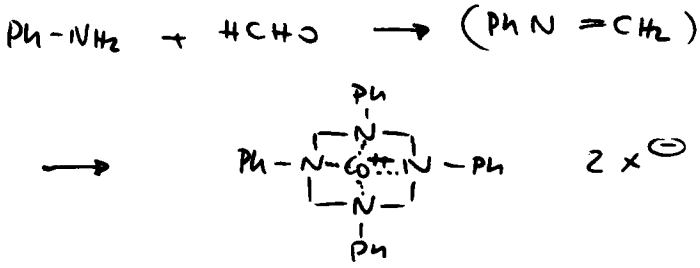
5.8 Investigations on the "Roumanian Approach" and Experiments to Decomplexate the Complexes Formed

During our investigations, we have detected a paper published in 1973 by a Roumanian group of Bucurest being more or less "hidden" in their small University Bulletin[39].

These authors claim that reacting aniline and formaldehyde in DMF or DMSO adding Co^{2+} as template ions "1,3,5,7-tetraphenyl-1,3,5,7-tetraazacyclooctanes (TTO)" are formed besides "1,3,5,7,9,11-hexaphenyl-1,3,5,7,9,11-hexaazacyclododecane (HHO)" and "1,3..21,23-dodecaphenyl-1,3..21,23-dodekaazacyclotetraeicosane (DDTE)" depending on the molarity of the reactants.

Thus, "TTO" is formed when the ratio 1 Co : 6 aniline : 6 form-

aldehyde is employed, where $CoCl_2 \cdot 6H_2O$ is dissolved in the minimum amount of DMF, separately 2.72 ml aniline in 10 ml DMF and 2.14 ml formaldehyde in the same amount of DMF. This mixture is refluxed on the oil bath for 2 d and a pink solid substance is filtered off. The green solution is treated with EtOH and a grey light blue solid is precipitated, filtered and washed with EtOH:



We have tried to repeat this communicated tetramerization reaction as good as possible, although the details given are not too explicit, so that reproduction of this procedure turned out to be difficult; on the other side, we have ensured by a broad CA-on line literature search that this is the only publication of these authors on this object, and there exist no preceding or following papers.

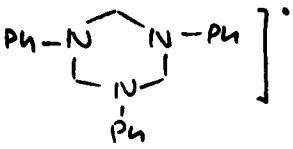
In few of a great number of repeating and modified experiments we were able to reproduce the original work, and in some cases we were able to isolate a green solid which has been studied. Employing high-resolution Mass Spectrometry we have found a molecular ion:

m/z 420.2101 showing an elemental composition

$C_{28}H_{27}N_4$ (calcd. 419.5540 ; i.e. M^+-1).

At least this MS (10^{-6} Torr, 230°C, 70eV) demonstrates that the complex formed is only weak, and the tetrazocine ligand

under the conditions applied is rather volatile. Due to its metastability additional fragmentation products have been found:



m/z 315

m/z 105

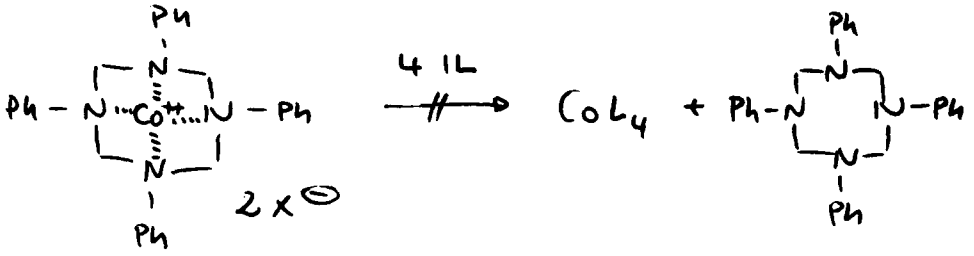
Thus, a formation of the 8-membered Co^{2+}-tetrazocine complex as claimed by the Roumanian authors seems to be true.

In the following it was tried to vary the conditions as well as the individual transition metal in order to attempt an optimization of this procedure, as shown in the following Table 5.

Table 5. Variations of the "Roumanian Approach"

Metal Salt	Conditions/Temp./Time	Results/Comments
$CoCl_2$	r.t.	violet solution; no reaction; salt recovered
	r.t. to 80°C	blue solution; amorph substance (mixture of paraformald. + Co-solvent complex)
	120°C; 8h to 2d	green solution: polymerizates
	150-160°C;2 to 6d	several experiments: either polym. compound or green powder recovered
	160°C; 2d	green solid (Complex) with correct MS
$Ni(Ac)_2$	80°C; 1d	no reaction
$NiBr_2$	120-160°C; 2-4d	polymeric material
$CuCl_2$	140°C; 8h to 3d	solid compound, but no crystals MS: no peak >m/z 200; could not be characterized
	160°C; 2-6d, DMF or DMSO or acetylacetone	polymeric materials

Since we were able to reproduce the sparely given Roumanian experimental conditions, we have now tried to remove the central metal ion being obviously only weakly bound in the complex. For this reason we have choosen stronger complexing ligands (1L):



This should deliberate the former ligand formed originally by the template effect: 1,3,5,7-tetraphenyl-1,3,5,7-octahydrotetrazocine. For this reason we have firstly tried to triturate the complex with several solvents of various polarity: pertoleum ether, benzene, methylenechloride, chloroform, acetonitrile, acetone, alcohols. But this did not lead to any characteristic compound.

Then, we have used stronger complexing agents, such as cyanide ions: KCN. To the solution of the complex equimoler amounts of CN^- were added dropwise, and an exothermic reaction was observed. The solution was decolorized to brownish yellow. After evaporation of the solvent and extraction of the residue with appropriate solvents (petroleum ether, methylenechloride, acetone) the t.l.c. showed in all cases complex mixtures consisting of numerous compounds. Accordingly, column chromatography did not lead to the isolation of any pure compound. Most of the components obviously decomposed further on the chromatographic material.

Variations of the conditions applied (smaller quantities of CN^-; different solvents, ice-cooling etc.) did not alterate the almost negative result.

Thus, it can be concluded that the Co-complex as described above has an only limited stability, so that in some experiments it was in fact possible to isolate it in substance. However, as soon as the stabilizing central atom is removed by stronger ligands, the resulting free tetraphenyl-tetrazocine undergoes at once decomposition and/or polymerization. Summing up, this "Roumanian approach" via complex formation seems to be not an

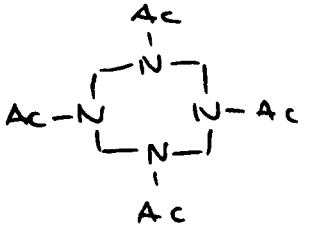
useful and valuable access to the TAT system.

6. Outlook and Consequences

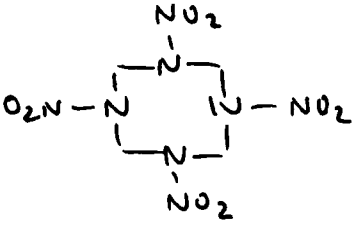
This research project has been carried out in very close and trustful cooperation with the Scientific Liaison, Dr. Everett E. Gilbert, and his colleagues, ARDC, Picatinny Arsenal, Dover, NJ. At least I visited once a year Picatinny Arsenal and communicated in several conferences and discussions with this group of US-Army Scientists about our recent results. Many of the experiments shown above have been recommended by Dr. E.E. Gilbert and his colleagues, and these advices and suggestions are gratefully acknowledged. Reports on these visits, conferences and discussions have been duly submitted to USARDSG(UK), London.

From these experimental results described above follows, there exists only a veyr small ridge pathway leading to several stable tetrazocines. Thereby, the stability of this 8-membered [8]-ane-N_4 system is strictly limited by steric, electronic and resonance factors. If the final molecule does not meet these requirements, instability, decomposition, and polymerization are the consequences.

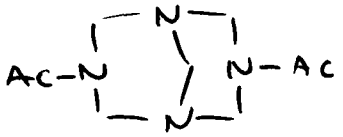
So far, only the following tetrazocine derivatives have been shown to posses sufficient stability for isolation and storage:



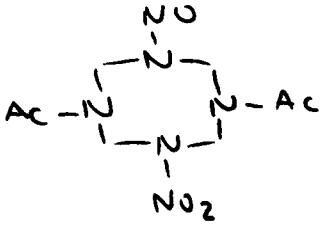
TAT



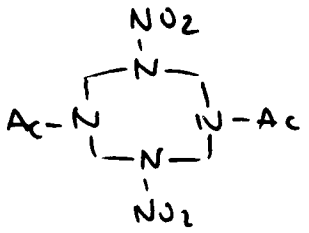
HMX



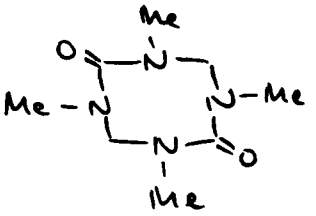
DAPT

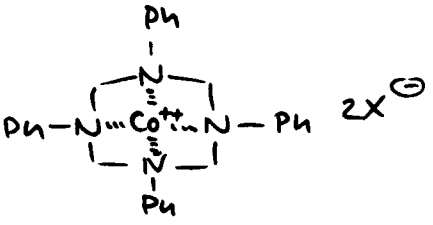


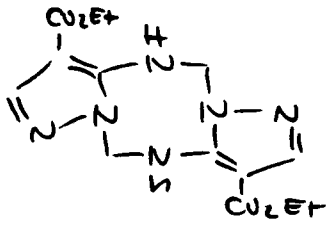
DANNO

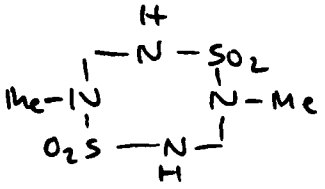


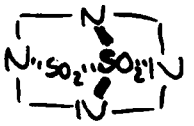
DADN











40)

Common feature of all these mono-, bicyclic and condensed tetrazocines is a stabilization induced by a strong mesomeric effect of the acetyl or nitro (nitroso) groups. In the X-ray structure shown on the example of TAT (cf. Fig. 1, page 5) the molecule exhibits a wavelike conformation with two (1,5) acetyl groups pointing upright (axial position) while the remaining (3,7) acetyl groups possess a horizontal (equatorial) position, which enables the substituents to have a minimum of steric interaction. The other derivatives of this TAT-type may behave similarly.

In the case of the cyclic ureides and the tricyclic bis-pyrazolo-tetrazocine, the amide resonance is built into the 8-membered ring, and as a consequence, the recently published X-ray analysis shows accordingly a planar conformation with the four N-methyl groups bent slightly out of the plane (tetraeder angle at N) while the amidic carbonyl groups are in-plane. From this structure it can be understood that all attempts to synthesize cyclic ureides of this type with more bulky substituents on N meet definite steric hindrance.

Finally, the "Roumanian" tetraphenyltetrazocine-Co-complex gains its stability from the ligand-metal ion interactions; the limited cavity of the tetrazocine thereby only allows Co^{2+} to be bound as central atom to a metastable complex. As soon as the central atom, however, is removed the remaining ligand is destabilized due to steric interactions of the few phenyl groups, and rapid decomposition is the only consequence.

The two SO_2-containing ureide and urotropine analogs behave similarly according to this pattern.

As another consequence of these forementioned stability requirements, only these accesses can be successful which lead in their reaction course to tetrazocines containing these mesomeric stabilizing substituents, such as N-acetyl, N-nitro or ring carbonyl groups.

Dr. Everett E. Gilbert, the permanent Scientific Liaison for this Contract, previous Chief of the Synthesis Section, Chemistry Branch, Energetic Materials, ARDC, Dover, NJ, and one of the leading experts in the field of TAT, HMX, DAPT, DADN syntheses, has expressed during the Conferences held at Picatinny Arsenal, Dover, NJ, on July 20/21, 1987 (cf. Report dated July 24, 1987) and July 13/14, 1988 (cf. Reprot dated July 21, 1988), after his decades-log experience in this rather complex and challenging field of tetrazocine synthesis, that he knows very well that efforts and significant innovative results are less a product of a relative short research period, but can only gained after an appropriate time of working in this field and getting more and more insight in the chemistry of formation and of stability of this rather unique class of heterocyclic 8-membered compounds. After this three years period, we want to confirm these predictions with emphasis.

As a result of this Cooperation Contract,we want to pursue within the novel Contract "New Synthetic Approaches to TAT" (R&D 4480A-CH 01, Contract No. DAJA 45-89-C-0003), which was awarded 6th December 1988, accordingly these pathways which are in agreement with the forementioned findings & consequences:

1) Investigation of the classical urotropine synthesis in

the presence of Ac_2O, AcOH, Cs^+ as catalyst, and with ß- and γ-cyclodextrins employing the molecular encapsulation technique.

2) Extending the Kadowaki procedure of cyclic ureas to dimethalurea.

3) Extending the cyclic ureide synthesis to methylenebisacetamide (MBA) in long-time experiments at room temperature.

4) To alkylate DAPT according to lit[11] with alkylhalides and to transfer the bis-acetyl-bis-alkyltetrazocines into TAT.

5) To degradate selectively the tricyclic dipyrazo-tetrazocine[18] after reduction in the system AcCl, AcOH, Ac_2O into TAT.

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8. Glossary

TAT	1,3,5,7-Tetraacetyl-1,3,5,7-octahydrotetrazocine
HMX	1,3,5,7-Tetranitro-1,3,5,7-octahydrotetrazocine
DAPT	3,7-Diacetyl-1,3,5,7-tetraazabicyclo[3.3.1]nonane
TRAT	1,3,5-Triacetyl-1,3,5-hexahydrotriazine
Cl_2PPh_3	Dichlorotriphenylphosphorane
Br_2PPh_3	Dibromotriphenylphosphorane
Me_3SiCl	Trimethylchlorosilane
TMSCl	" " "
NBS	N-Bromosuccinimide
PTA	para-Toluenesulfonic acid
t-Bu	tert. Butyl
TFA	Trifluoroacetic acid
MeCN	Acetonitrile
DADN	1,5-Diacetyl-3,7-dinitro-1,3,5,7-octahydrotetrazocine
DANNO	1,5-Diacetyl-3-nitro-7-nitroso-1,3,5,7-octahydrotetrazocine
MBA	N,N'-Methylenebisacetamide
DCC	Dicyclohexylcarbodiimid
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
NEt_3	Triethylamine
BuLi	n-Butyllithium
Me	Methyl
Et	Ethyl
Ph	Phenyl
Ac	Acetyl
AcCl	Acetylchloride

Ac_2O	Acetanhydride
$AlCl_3$	Aluminium chloride
Δ	Heating conditions
r.t.	Room temperature
d	Days
h	Hours

9. Appendixes

9.1 EXPERIMENTAL PART

Synthesis of DAPT

In a 250 ml three-necked flask fitted with a dropping funnel, 14 g of urotropine and 6.2 g of ammonium acetate are suspended in 7 ml water. The mixture is cooled to 5-10°C and over a period of 1 h 30.6 g acetanhydride are added dropwise. After stirring for additional 30 min at 10°C, the reaction mixture is evaporated to dryness. The residue is crystallized from acetone.
Yield: 19.8 g (93%); mp 192°C.

Synthesis of TAT from DAPT with Thionylchloride

In a 250 ml three-necked flask equipped with reflux condenser, dropping funnel, and thermometer are placed 3 g of thionylchloride 2 g of ammonium acetate, and 1.5 ml of H_2O solved in 100 ml of acetanhydride. After stirring for 15 min, the solution is cooled to 5-10°C and 5.3 g of DAPT solved in acetanhydride are dropwise added. After warming up to room temp. with continued stirring, all volatile material is distilled off in vacuo. The residue is crystallized from ethanol. Yield: 3.73 g (53%); mp 153°C (Lit.[5] 153-158°C).

General Procedure for the Reaction of Urotropine and DAPT in the System Triphenylphosphane/Hexachloroethane

In a 500 ml flask fitted with a reflux condenser and in an Argon atmosphere, 7 g of urotropine/10.6 g of DAPT are solved in 300 ml of methylenechloride. To this solution are added: in the case of urotropine 26.2 g of PPh_3, 10 g of triethylamine, 12 g of hexachloroethane, and 51 g of trimethylsilylchloride; in the case of DAPT 13.1 g of PPh_3, 5 g of triethylamine, 6 g of hexa-

chloroethane, and 25 g trimethylsilylchloride.

The reaction mixture is slightly warmed during 1 h with monitoring the reaction course with t.l.c.. After cooling to 15°C, the precipitated thiethylammonium chloride is filtered off and the filtrate is evaporated. The t.l.c. of the residue (ethanol/CH_2Cl_2 = 1:1) shows the complete decomposition of the educts to give nonidentificable products. Adding a base (NaOH) the smell of ammonia can be registered.

General Procedure for the Reaction of DAPT with Organic Halides

In a 250 ml flask fitted with reflux condenser and gas inlet, 10.6 g of DAPT and 9.3 g of t-butyl chloride or 21 g of chlorosulfonyl chloride, or 19 g of p-toluenesulfonyl chloride, respectively, in 150 ml solvent (cf. Table) are mixed, then addition of 13.5 g $AlCl_3$ follows in several portions. Under Argon atmosphere the mixture is stirred firstly at room temperature, then under slight warming (monitoring by t.l.c.). After 2 h the solution is concentrated to dryness in vacuo. As t.l.c. shows greater amounts of unchanged DAPT besides some decomposition products are present. No separation or characterization was possible.

Halogenide	Solvent
t-BuCl	petroleum ether, methylenechloride or t-BuCl as solvent
$ClSO_2Cl$	acetylchloride
$pTsSO_2Cl$	ethyl acetate, acetanhydride

Reaction of Methylenebisacetamide (MBA) with Formaldehyde

In a 250 ml flask 29.5 g of MBA, 10 g of an aq. 38% formaldehyde solution and few drops of cc. H_2SO_4 are solved in 100 ml water and refluxed for 1 h. After concentration of the solution in vacuo, t.l.c. (aceton/Methylenechloride = 1:1) shows the formation of some TAT.

Synthesis of Cyclic Ureides According to Kadowaki[22a)]

In a 250 ml flask, 100 mmol of N,N'-dialkylureas and 1.5 g of $Ba(OH)_2$ are solved in 24 ml 38% aq. formaldehyde solution and warmed up to 70°C for 10 min. After removal of the water, a

a slurry substance is obtained which was treated with 150 ml of MeOH, neutralized with HCl and filtered. After evaporation of MeOH the residue is crystallized from ethanol.

For N,N'-dimethylurea: 1,3,5,7-Tetramethyl-1,3,5,7-hexahydro= tetrazocane-2,6(3H,7H)-dione; yield: 1.1 g (11%); mp 259°C; $C_8H_{16}N_4O_2$ (2oo.2) MS (70 eV): m/z 200 (M^+).

Reduction of the Bisureide with $NaBH_4/LiBH_4$- THF, TMSCl

In a 25o ml flask equipped with reflux condenser, dropping funnel, and gas inlet, o.8 g of $NaBH_4$ (o.45 g of $LiBH_4$) are solved in 100 ml of absol THF; then addition occurs of 4.5 g of TMSCl (with $NaBH_4$: solution is kept at r.t.; with $LiBH_4$ the solution is cooled to 10-15°C). The mixture is moderately warmed until precipitation of NaCl is complete. Then 1 g of the bisureide, solved in THF, is added, and then 30 min gently refluxed. After cooling to ambient temperature, 30 ml of a methanolic Na_2CO_3-solution are added, and the solvent is finally evaporated. The residue is filtrated under Argon, the etherical solution is concentrated in vacuo and the residue checked with t.l.c. (CH_2Cl_2. In the sresidue of the $NaBH_4$-reduction 1,3,5-trimethyl-1,3,5-tetrahydrotriazine-2-one is identified with the aid of MS. In the $LiBH_4$-system only decoposition products have been found.

Synthesis of t-Butyl-methyleneimine

22.5 g (275 mmol) of a 37% aq. formaldehyde solution is added dropwise with running water cooling to 18.25 g (250 mmol) of t-butylamine. After the exothermic reaction has ceased, the mixture is stirred for 0.5-1 h with addition of few pellets of KOH, after few minutes the solution is filtered. The organic layer is separated and distilled. The product has a bp_{760} = 66-68°C; yield: 25-45%. The residue is almost polymeric material. - As the t-butylmethyleneimine is decomposing after a short time, it may be immediately used for further reaction steps. (Side reaction: formation of 1,3,5-tris-t-butyl-1,3,5-hexahydrotriazine).

Synthesis of the"Green Complex" Following the "Roumanian Approach"

2.38 g (25 mmol) of $CoCl_2 \cdot 6\ H_2O$ is solved in 50 ml of DMF to give a violet solution. 13.95 g (150 mmol) of aniline in DMF and

12.5 g (150 mmol) of formaldehyde solved in some DMF are added dropwise. After short time a blue color and fading of the solution appears. The reaction mixture is now heated slowly until 160°C; after some h a green color appears. After keeping 2 d at this temperature the mixture is cooled to ambient temperature. Filtration gives some unchanged violet Co-salts. Evaporation of the solvent gives a green solid compound, which could be further analyzed.

9.2 LIST OF PUBLICATIONS

There have no publications appeared from our side concerning this research project.

9.3 LIST OF PARTICIPATING SCIENTIFIC PERSONNEL

(1) Dr. Marcus Bongen, Dipl.-Chem.
Dr. Bongen made his PhD-Thesis entitled:
"Experimentelle Studien zur Synthese des 1,3,5,7-Tetraacetyl--1,3,5,7-octahydrotetrazocins und verwandter achtgliedriger 4-N-Heterocyclen" in the course of this Research Project.
The Mathematisch-Naturwissenschaftliche Fakultät has awarded the PhD-degree on the basis of this Thesis.

(2) Dipl.-Chem. Johannes Nagelschmitz
Mr. Nagelschmitz works as the second Research Scientist within this Project, and he has been nominated also for the next Research Project and Contract DAJA 45-89-C-0003 R&D 4480A-CH-01, and he is planning to take parts of his results into his futural PhD-thesis.

*) Additional remark:

ref: chapter 5.5 p. 21

In this regard it is worthwile to mention that Koppes et al.[35] have found that the stability of this ring system varies widely with the nature of the substituents. N-Alkyl derivatives destabilize this system, while the tetraacetyl derivative shows considerable stability, but hydrolysis or nitrolysis failed on this derivative. Only the 2,2,5,5-tetra(trifluormethyl)-imidazolo[4,5-b]imidazole gave the tetranitro derivative. This behaviour reflects once again the rather selective reactivities of this class of compounds, and accordingly of the tetrazocines which have been found to be only stable as TAT or HMX. No experiments are known so far to split the central σ-bond of this class in order to get TAT on this way.