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PHOTOCHEMISTRY AS A TOOL IN HETEROCYCLIC SYNTHESIS. FROM PYRIDINIUM N-YLIDES TO DIAZEPINES AND BEYOND.

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In the first part of this review we shall describe some industrial applications of photoinduced heterocyclic syntheses via singlet oxygen and via free radicals.
The second part is dealing with large bench-scale synthesis of 1,2-diazepines which are thence used as building stones for the synthesis of some new polyheterocyclic systems.

1 Introduction.

2 Photochemistry as a tool in heterocyclic synthesis on an industrial scale.

- Reactions with photoinduced singlet oxygen leading to ascaridole and to rose oxide.
- Photoinduced fragmentation for light-curable coatings and photooximation of cycloalcanes.

3 Photochemical synthesis of 1,2-diazepines on a large bench-scale using a dynamic thin film photoreactor.

4 Diazepines as synthons for the build-up of polyheterocyclic molecules: homodiazepines, bicyclic β-lactams, polyazaazulene-derivatives.

INTRODUCTION

Organic photochemistry has blossomed during the last twenty years from an insignificant bud into the blossoming of a scientific discipline which is well established by now. The subject continues to expand at a tremendous rate (1,2,3). New, and sometimes highly specific reactions are discovered which find increasing application in organic synthesis (4). Nevertheless it proves quite impossible to be encyclopaedic in a concise treatment of the subject.

Industrial applications of photochemical processes are not legion for the time being. Photochemistry after all is but one of the many means of producing chemical compounds or bringing them into reaction. However it has some advantages over thermal, catalytic and other methods that immediately fascinate the industrial chemist (5):

- Selective activation of individual reactants;
- Specific reactivity of electronically excited molecules;
- Low thermal load on the reaction system;
- Exact control of radiation in terms of space, time and energy.

But photochemistry is not without its own specific problems:

- Only absorbed light can be exploited for chemical purposes. For this reason many reaction systems are ruled out for photoreactions because of their unfavourable absorption characteristics;

- Photoreactions may be rapidly terminated if products with competing absorptions are formed;
- Photochemical production plants may incur high unit capital costs if the space-time yield is low as a result of limitations imposed by the power of the lamps;
- Eventually it should be stressed that light is more expensive than heat because considerable losses occur in the production of electrical energy and in its conversion into usable light energy.

PHOTOCHEMISTRY AS A TOOL IN HETEROCYCLIC SYNTHESES ON AN INDUSTRIAL SCALE

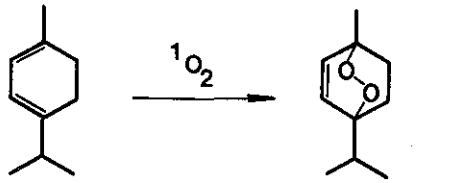
Photochemistry as a tool in heterocyclic synthesis has had some applications in modern chemical industry.

1. Reactions with photoinduced singlet oxygen

Singlet oxygen, which is produced via a photosensitized process has been shown by professor G.O.SCHENCK to lead to three reaction patterns which cannot be achieved with ordinary triplet oxygen (6):

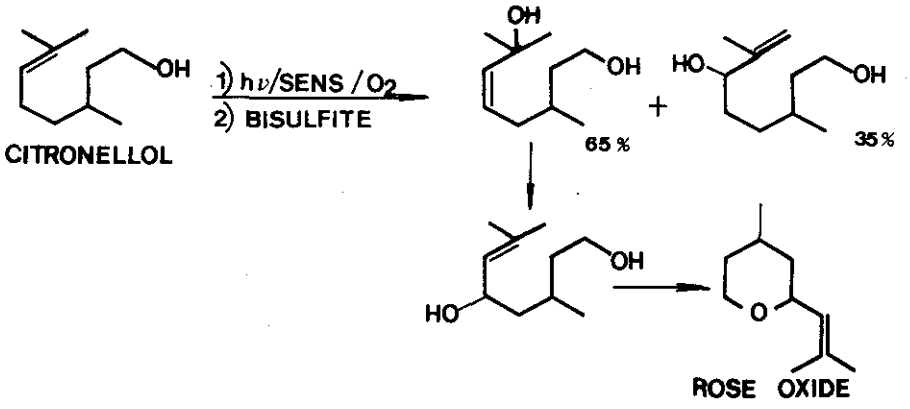
- diene-reactions;
- ene-reactions;
- [2+2]-cycloadditions.

After the Second World War the diene reaction leading from α-TERPINENE to ASCARIDOLE had been carried out on a technical scale. At that time ascaridole had some significance as an anthelmintic, and previously it could only be obtained from the natural oil of CHENOPODIUM.



α-TERPINENE ASCARIDOLE

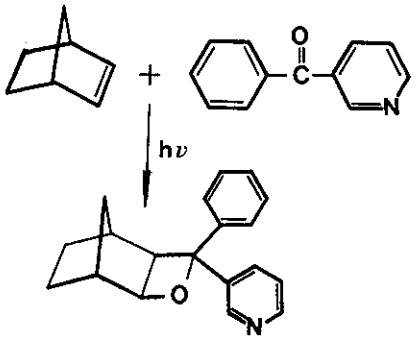
The ene-reaction with singlet oxygen is being used by two perfumery manufacturers, DRAGOCO in West Germany and FIRMENICH in Switzerland, for the synthesis of ROSE OXIDE starting from CITRONELLOL (7). A mixture of secondary and tertiary hydroperoxides is obtained by the photooxidation of citronellol in the presence of ROSE BENGAL as a sensitizer. Reduction of this mixture with bisulfite yields the corresponding alcohols. Allylic rearrangement of the main product in acid solution and subsequent dehydration leads to a mixture of the stereoisomeric rose oxides, which are used as perfumes.



2. Photoinduced cycloaddition reactions

The gap between the results of academic research and their practical exploitation is enormous in the field of photoaddition. One reason for the poor technical exploitation of photoaddition reactions might be due to the fact that there is not enough cooperation between industrial chemists and photochemists.

Thus even the elegant cycloadditions of carbonyl compounds to olefins (8) have only led to patent applications and, to our knowledge, not to any single commercial product as yet.



PATENT APPLICATIONS ONLY:
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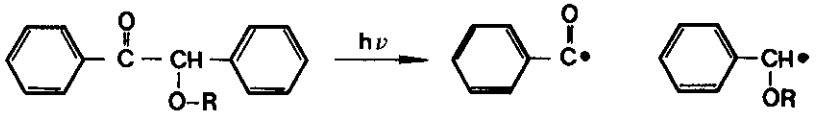
DOS 1520 640 (1956)

3. Photoinduced fragmentations as a tool in heterocyclic syntheses. Photochemically induced fragmentation has penetrated further into industrial chemistry than any other primary photochemical process. Applications range from initiator systems for light-curable coatings and printing inks to the commercial scale photooximation production processes.

A - Light-curable coatings. Photoinitiators are used in order to induce photopolymerization and photocrosslinking on an industrial scale (9), fragmentation being the primary photochemical step.

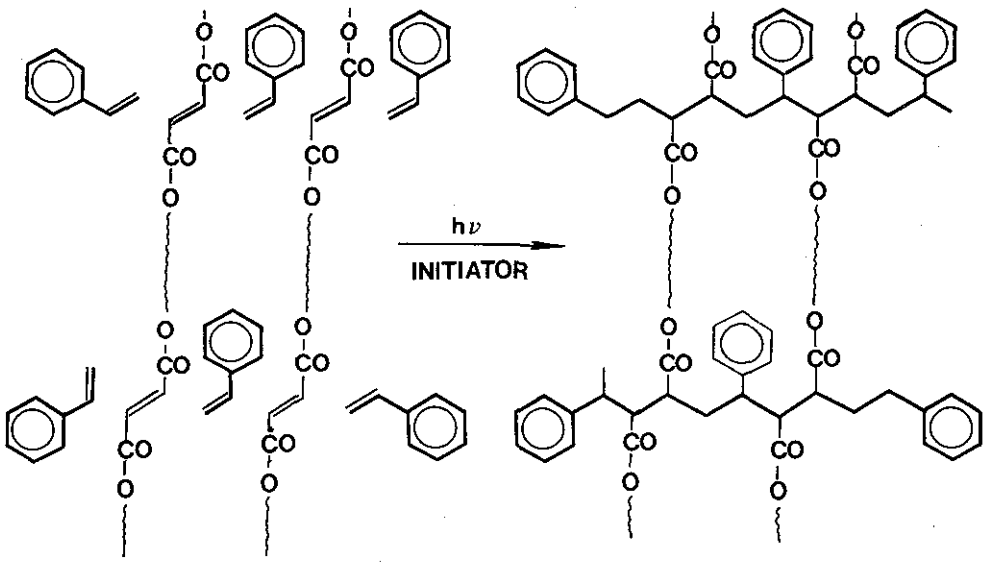
Photopolymer systems are mostly used for UV-curable coatings (10). These are systems in which exposure to light brings about changes in physical properties (solubility, adhesion, mechanical strength). They are mainly used in the furniture, printing and electronic industries.

INITIATORS FOR LIGHT—CURABLE COATINGS

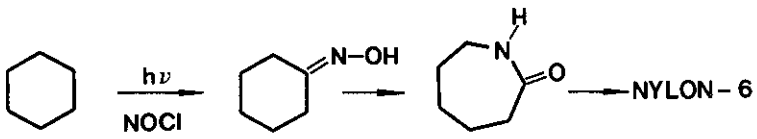


BENZOIN ETHERS

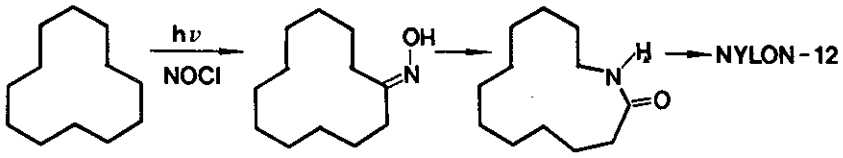
The photoinitiator, for example benzoin ethers, splits into radicals which induce crosslinkage of the polyester chains as a result of copolymerization of styrene with the double bonds of fumaric acid.



B- Photooximation. The technical realization of photooximation is probably the most important event which occurred during the last ten years in industrial photochemistry (11). Although photooximation has been known since 1919 (12), the industrial breakthrough occurred in Japan only about ten years ago when TOYO RAYON introduced the photoinduced ε-caprolactam synthesis which operated in 1975 on a 150.000 tons-a-year scale. This is quite remarkable since the risk had to be taken of launching a commercial scale photoreaction process, with a quantum yield of less than unity, for a product that sells at about 1 to 2 $ per kilogram.



Since then the French company SNPA has taken a plant on stream for producing about 5000 tons-a-year of lauryl lactam as the precursor of NYLON-12.



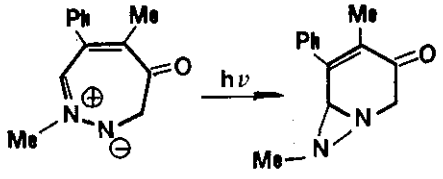
These encouraging examples demonstrate that we are technologically in a position of carrying out photoreactions which can compete with conventional and cheap processes. Therefore it would seem to me that photochemical processes should have an even brighter future when it comes to more elaborate syntheses for example in the pharmaceutical industry.

PHOTOCHEMICAL SYNTHESES OF 1,2-DIAZEPINES ON A LARGE BENCH SCALE

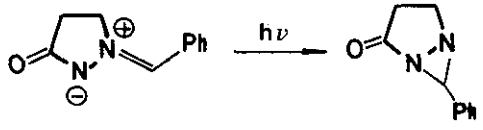
Having reviewed briefly some industrial applications of photoprocesses in the field of heterocyclic synthesis, I would like to focus now on a photoinduced ring expansion reaction we have found about ten years ago in Mulhouse (13). I shall describe in the first place the photochemical and highly specific rearrangement of 1-iminopyridinium ylides into 1,2-diazepines on a preparative scale. Eventually we shall be dealing with the many applications of 1,2-diazepines on their way to polycyclic systems.

Electrocyclic ring closure of azomethine-imines -which are 4π 1,3-dipolar species- to the corresponding diaziridines is permitted, both by thermal and by photochemical processes according to symmetry selection rules (14). Stable azomethine-imines, which

are only but a few, lead photochemically to the corresponding diaziridines as was shown by Moore (15) and by Schultz (16).

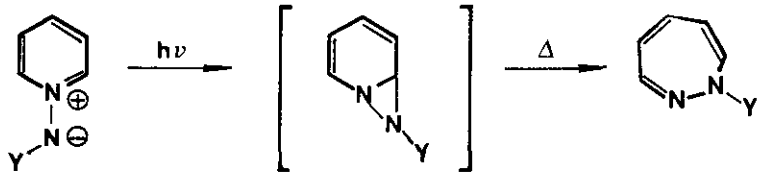


MOORE 1968



SCHULTZ 1970

Mesoionic 1-iminopyridinium ylides, in which Y is an electron attracting chromophore, can be considered in a formal way as aromatic azomethine-imines. Indeed they behave as such: thermally they undergo 1,3-dipolar cycloaddition reactions (17) and isomerize to 1,2-diazepines when excited by UV light (13,18,19,20). Such photoinduced ring expansions are best explained by assuming



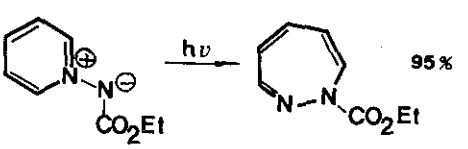
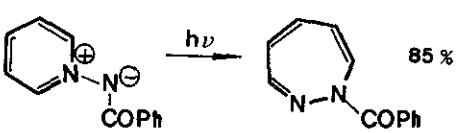
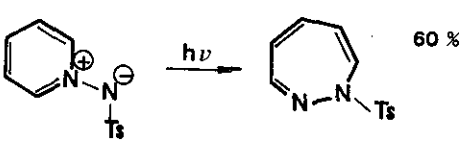
an electrocyclic reaction, leading to an intermediate 1,7-diazanorcaradiene, followed by a thermal disrotatory valence tautomerization which yields the seven-membered diazepine.

The synthesis of the zwitterionic and colourless pyridinium ylides is based on nitrogen-nitrogen coupling reactions. They invol-

ve nitrene derivatives, which are obtained from azido compounds like ethyl azidoformate (21), or O-sulfonylated hydroxylamines, like hydroxylamine-O-sulfonic acid (22) or, even better, mesitylsulfonylhydroxylamine, a reagent which has been developed by professor Tamura (23).

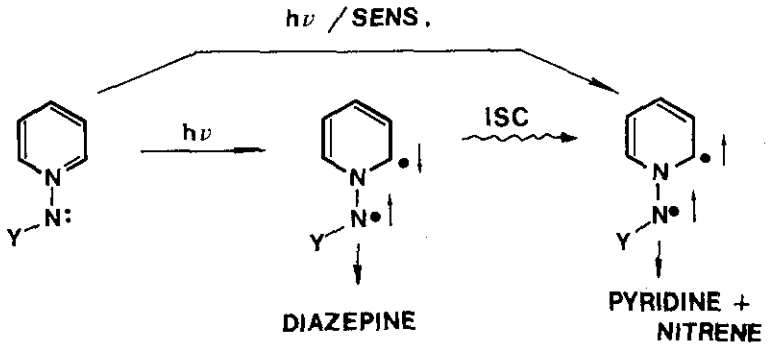
Various chromophores have been attached to the pyridine nitrogen atom: alkoxycarbonylimino-, benzoylimino- and tosylimino- groups. All ylides lead in high chemical yield to the corresponding 1,2-diazepines (Table 1) when irradiated by means of high pressure mercury vapour lamps through Pyrex glass. As can be seen from Table 1 1-iminopyridinium ylides have a strong absorption band which appears at about 320 nm. in methanol solution. A strong negative solvatochromism is observed which is typical of all pyridinium ylides and which is indicative of an intramolecular charge transfer process. Let us mention that the empirical solvent polarity scale, as defined by Kosower (Z parameters) and by Dimroth (E_T parameters) has been set up by using a zwitterionic species which is an arylogue of a substituted pyridine-N-oxide (24).

Table 1: Absorption spectra, blueshift and photochemical ring enlargement of some 1-iminopyridinium ylides

λ_{max} nm (ε)	
316 (5,000) in MeOH	 95 %
344 (5,300) in C_6H_6	 85 %
319 (5,000) in MeOH)	 60 %
322 (3,800) in MeOH	

The photoinduced ring enlargement of 1-iminopyridinium ylides leads *in most* cases and <u>in high chemical yield</u> to the corresponding 1,2-diazepines. The photolytic N-N bond cleavage occurs only as a negligible side-reaction. To the contrary no diazepine is formed when triplet sensitizers like eosine are used, the only detectable pathway being N-N bond cleavage!

From these results we conclude that the photolytic N-N bond cleavage operates via an excited triplet state (25) and that an excited singlet state is responsible for the ring expansion process (26).



Chemical yields of diazepine formation being high, it was of interest to prepare these seven-membered rings on a large scale. As a matter of fact 1,2-diazepines proved to be excellent synthons for the syntheses of more elaborate polycyclic systems. A 2000 watt dynamic thin film reactor was used for this purpose. It permits the easy preparation of up to 40 g of diazepines in a one-batch-one-day procedure. In order to suppress any undesirable thermal side-reactions, the solution is externally cooled to about +10°C.

As to the overall quantum yield, it is low indeed: about 3%. Since diazepines are practically the only reaction products formed, this very small quantum yield is indicative of a competing radiationless thermal process. Furthermore we found that on heating in DMSO-d^6 N-benzenesulfonyl- and N-benzoyldiazepines revert

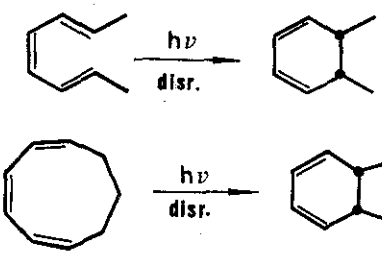
quantitatively back to their corresponding N-iminopyridinium ylides. A study of the kinetics of these reactions showed the process to be 1st order and the following activation parameters were derived (Table 2).

Table 2: Activation parameters derived from the thermal isomerisation of 1,2-diazepines to the corresponding 1-iminopyridinium ylides

3-methyl-diazepines Y	ΔH^* Kcal/mole	ΔS^* e.u.
SO_2Ph	23.7 ± 0.2	- 7.1 ± 0.6
CO Ph	26.5 ± 0.2	- 7.7 ± 0.3
COp-C_6H_4-Cl	25.4 ± 0.2	-10.2 ± 0.3

These values for ΔH^* and ΔS^*, together with the absence of any appreciable solvent effects, point to a concerted disrotatory closure of diazepines to the corresponding diazanorcaradienes in the rate determining step (27). The above results are in good agreement with those found by Winstein for similar processes (Schema 1) (28).

Scheme 1



ΔH^* ΔS^*

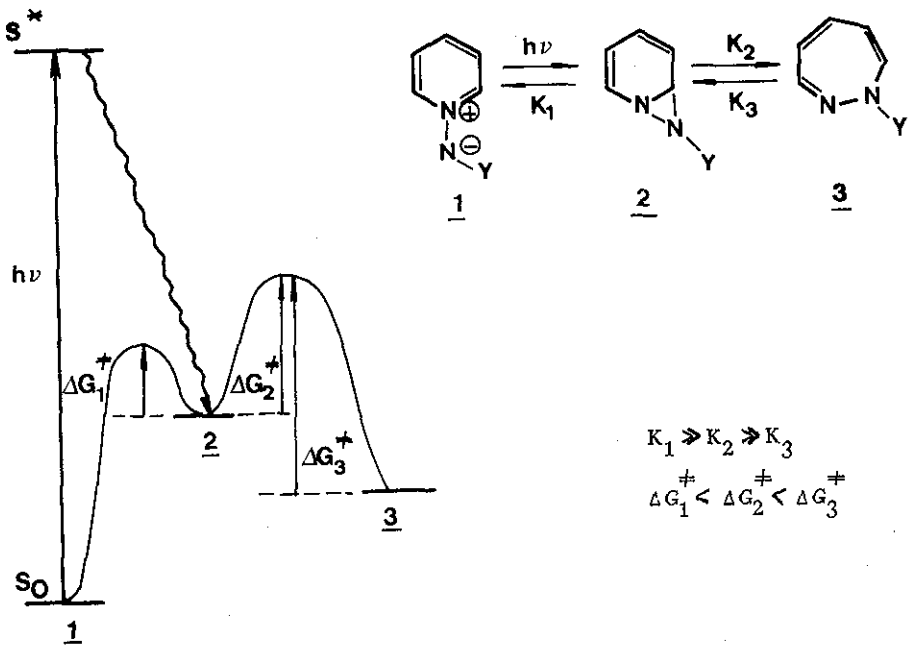
28.6 Kc/m - 7 e.u.

23.0 Kc/m - 4.7 e.u.

From these quantum yield and kinetic measurements the following reaction scheme can be derived which accounts for all qualitative and quantitative data we have collected so far (Scheme 2). The low overall quantum yield of the photoinduced conversion 1→3 is probably due to the fact that K_1 is about 30 times greater than K_2, provided that no radiationless deactivation proceeds from S_1 to S_o.

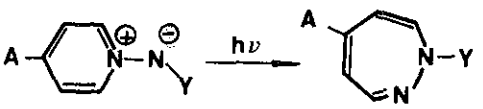
ΔG_3^*, being far greater than ΔG_1^* and ΔG_2^*, cannot be attained at room temperature ... otherwise diazepines would not be formed! Once ΔG_3^* is obtained by thermal activation, the reaction proceeds to the diazanorcaradiene 2 in the rate determining step and thence to the ylide 1. Such a reaction scheme obviously precludes any equilibrium to occur at room temperature between diazepines 3 and their norcaradiene tautomers.

Scheme 2



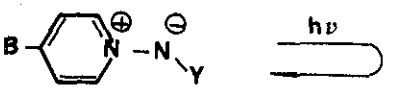
Ring monosubstituted pyridinium ylides are of interest to test substituent effects upon their photochemical reactivity. From data collected on Table 3 we deduce that the mesomeric effect of substituents attached to C-4 of the pyridinium ylide ring is pronounced indeed: electron-donating groups like dimethylamine, chlorine and phenyl permit photoinduced ring expansion, whereas electron-attracting groups like ketones, esters or nitriles inhibit this process (13,18,19,20).

Table 3: Photochemical behaviour of 4-substituted 1-imino-pyridinium ylides



Y = COPh or CO_2Et

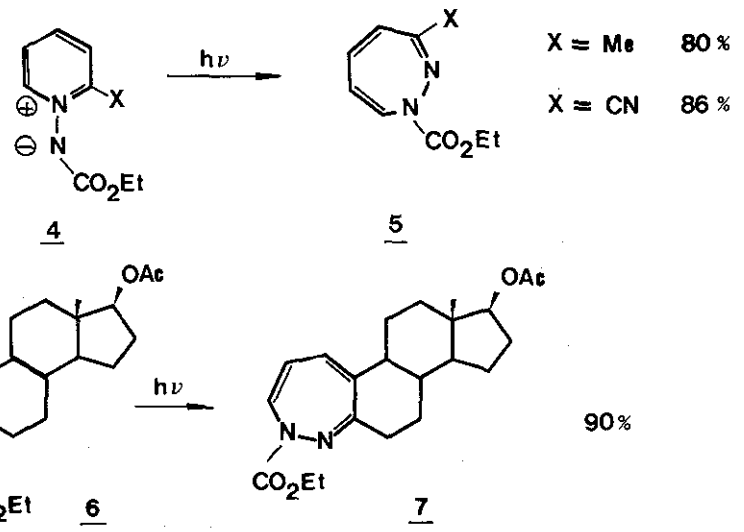
A = CH_3	75%
A = C_6H_5	90%
A = Cl	80%
A = N Me_2	65%



Y = COPh or CO_2Et

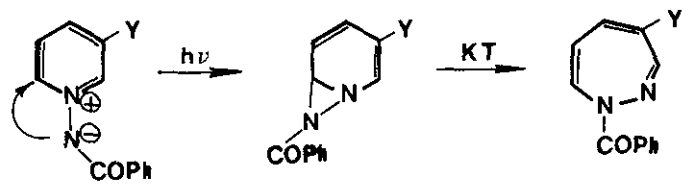
B = CO_2Et
B = CN
B = COAr

Substituents attached to C-2 or to C-3 of the pyridinium ring could lead to two isomeric diazepines depending upon the cyclisation direction of the exocyclic nitrogen atom: toward C-2 or toward C-6. 2-Chloro- or 2-methoxypyridinium ylides could not be synthesized. 2-Cyanopyridinium ylide 4 (X = CN) undergoes in high yield a regiospecific ring enlargement leading exclusively to 3-cyano-1-ethoxycarbonyl-1,2-diazepine 5 (X = CN) (13,18,19,20). Rather unexpectedly the 2-methylpyridinium ylide 4 (X = CH_3) leads to the same type of result: again one observed a regiospecific ring enlargement to 1,2-diazepine 5 (X = CH_3). Methyl groups having no pronounced electronic effect upon π electrons, it is assumed that the regiospecific ring enlargement is mainly due to a steric effect which would prevent ring closure of the exocyclic nitrogen atom to occur toward C-2. Along these same lines the steroidal 1,2-diazepine 7 could be synthesized regiospecifically and in high yield from ylide 6, this latter compound having been obtained in several steps starting from 19-NOR-testosterone(29).



3-Substituted pyridinium ylides are obviously devoid of any such steric interference during the diazanorcaradiene formation step. Therefore it was assumed that π electronic effects would not be hampered by steric interference. As can be seen from Table 4 electron-attracting groups like esters, amides and nitriles lead regiospecifically and in high yield to only one type of photoisomer, namely 4-substituted 1,2-diazepines. Up to now no satisfactory explanation can be put forward in order to account for this regiospecific ring expansion (30).

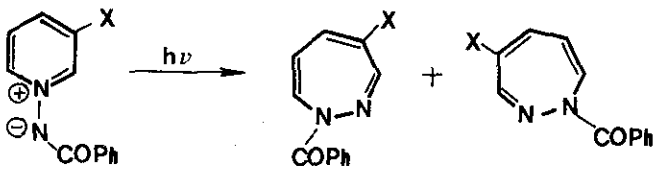
Table 4: Regiospecific photochemical ring expansion of 3-substituted pyridinium ylides (Y = π electron-attracting groups)



Y = CO_2Et (80%) Y = $CONH_2$ (86%) Y = CN (84%)

To the contrary, electron-donating C-3 substituents, which do not bear any acidic hydrogen atoms, lead in a non-regiospecific way and in high yield to a mixture of the corresponding 4- and 6-substituted 1,2-diazepines (Table 5) (30).

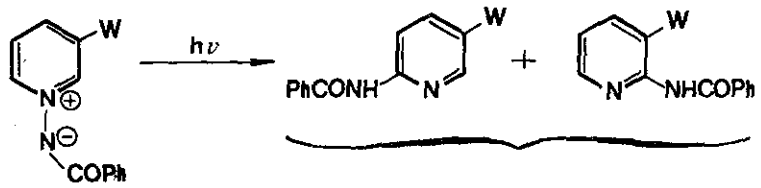
Table 5: Non-regiospecific photochemical ring expansion of 3-substituted pyridinium ylides (X = electron-donating groups)



X = F	80%
X = Cl	75%
X = Br	80%
X = OCOPh	74%
X = CH_3	70%

The photochemistry of 3-substituted pyridinium ylides, which bear acidic hydrogen atoms at the site of the electron-donating groups, do not lead to any diazepines. Instead one obtains a mixture of two isomeric 2-aminopyridines as can be seen from Table 6. The formation of these two types of isomers can be explained in terms of a non-regiospecific electrocyclisation of the exocyclic nitrogen toward C-2 and toward C-6, followed by a phototropy and the opening of the norcaradiene diaziridine rings. Alternatively one may also assume a non-regiospecific photoinduced 1,2-sigmatropic shift of the benzoyl-imino group to C-2 and C-6, followed by a prototropy (30).

Table 6: Non-regiospecific photochemical isomerisation of 3-substituted pyridinium ylides leading to 2-aminopyridines.



W = OH	50%
W = NH_2	60%
W = NHCOPh	55%

I,2-DIAZEPINES AS SYNTHONS FOR POLYHETEROCYCLIC-MOLECULES-BUILD-UP.

1,2-Diazepines, being easily available by the aforementioned photoprocess, proved to be interesting synthons for the construction of various polyheterocyclic systems by means of cycloaddition reactions. We shall describe briefly cycloaddition reactions upon the imine- and upon the Δ^4 and Δ^6 olefinic double bonds. From the X-ray diagram, as determined with 1-tosyl-1,2-diazepine, the following geometric parameters could be derived (31):

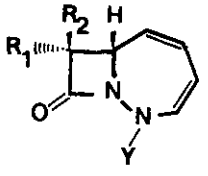
- as expected the molecule has a boat-shaped conformation;
- the N=C double bond measures only 1.262 Å, a result which seems to point to a non-conjugated imine function;
- the rest of the sp^2 carbon skeleton, although non planar in the solid state, shows a conjugation comparable to the one found in 1,3-cycloheptadiene.

We expected therefore some site-specific, concerted and non-concerted, cycloaddition reactions upon the imine and the Δ^4-double bonds. Furthermore cycloaddition reactions could proceed in a regiospecific manner. Site-specificity and regio-specificity were clearly the target of our investigations. Eventually we had in mind the synthesis of polyazaazulenes.

1. Cycloaddition reactions upon the imine double bond

Treatment of 1,2-diazepines with acetic acid chloride derivatives in the presence of triethylamine leads stereospecifically to the trans β-lactam adducts (Table 7) (32). It is commonly believed that ketenes are formed which add to the imine double bond via a zwitterionic intermediate, thereby permitting the formation of the thermodynamically less crowded trans β-lactam (33).

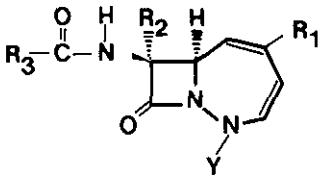
Table 7: Synthesis of β-lactams by cycloaddition of ketenes upon 1,2-diazepines



Y	R_1	R_2	Yields
CO-C_6H_5	H	Cl	70%
CO-C_6H_5	Cl	Cl	80%
CO_2Et	H	Cl	70%
CO_2Et	H	C_6H_5	56%
CO_2Et	Cl	Me	43%) 49%
CO_2Et	Me	Cl	6%)
CO_2iPr	H	Cl	80%

Altering the structure of natural products, in order to induce specific modifications of their pharmacological spectrum, is a general trend in modern drug research (34). In the particular case of β-lactam antibiotics, the thiazoline and thiazine moieties of penicillins and cephalosporins respectively have been replaced by other heterocycles (35). For example specific pharmacological properties have been found with 1-oxa- and 1-carba-cephalothins which have been prepared by various total synthetic methods (36). Along these lines we undertook

the total synthesis of cephalosporin analogues, of general formula 8, bearing a seven-membered ring fused to the β-lactam moiety.



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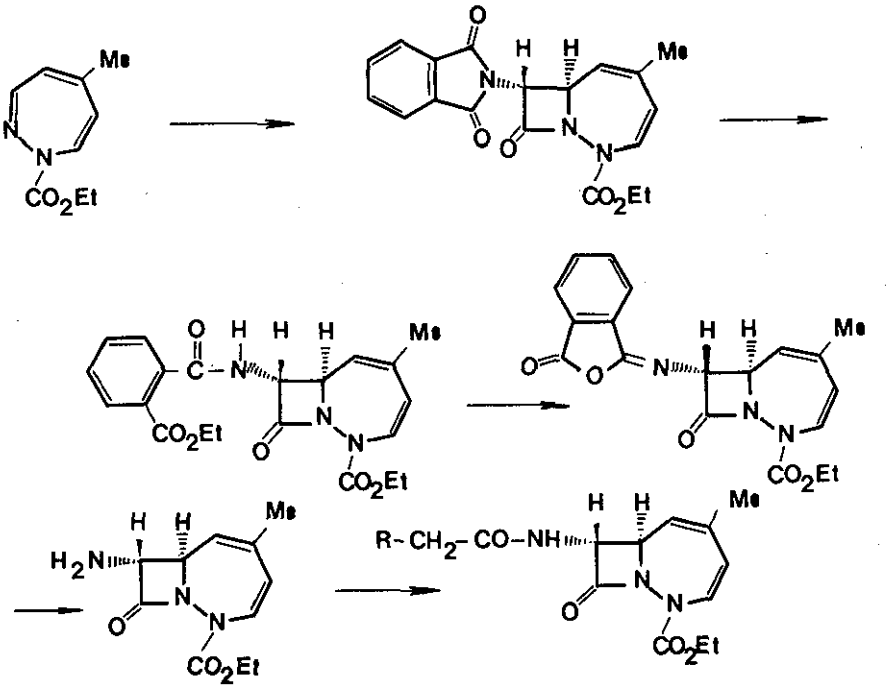
In a typical, although still incomplete, sequence (Scheme 3) we synthesized compounds of type 8 which are antibiotic analogues having the wrong configuration at the C-8 asymmetric center (37). The overall yield for the benzyl-ether derivative

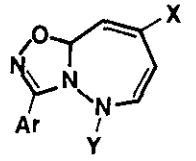
Scheme 3



R=C_6H_5-; p-NO_2-C_6H_4; C_6H_5-O; α-thiophenyl

is 57%, yield starting from the corresponding 5-methyldiazepine. Therefore we believe that the synthetic approach described in this scheme is a promising one. Configurational inversion of C-8 and introduction of an acid bearing group will be our next goal.

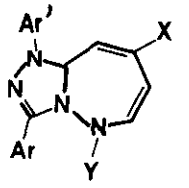
Nitrile oxides also add site-specifically and regio-specifically to the imine double bond of diazepines leading to the corresponding 1,2,9-triaza-8-oxabicyclo[5.3.0]-3,5,9-decatriene derivatives 9 in about 60% yield [X=H, CH_3 or C_6H_5; Y=CO_2Et or COC_6H_5; Ar = mesityl or phenyl] (38). With benzonitrile-oxide we isolated, besides the monoadducts 9,



9

bis-adducts (upon the Δ^2 and Δ^4 double bonds), a result which clearly indicates a higher reactivity of the imine double bond when compared to the olefinic Δ^4 double bond.

Eventually nitrile-imines, which are prepared <u>in situ</u> from benzhydrazide chlorides in the presence of triethylamine, add site-specifically and regio-specifically to the imine double bond of 1,2-diazepines. Triazoline derivatives 10 are obtained thereby in about 35% yield [X = H or CH_3; Ar = C_6H_5; Ar'=p-NO_2-C_6H_4; Y = COC_6H_5] (39).

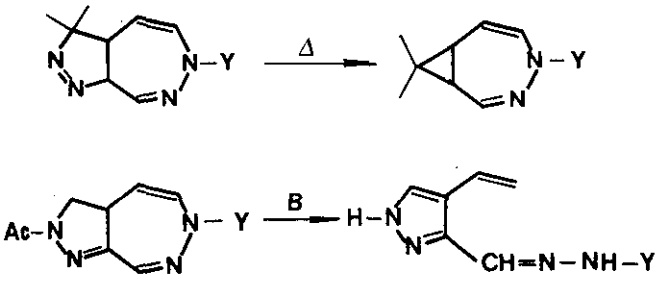


10

2. Cycloaddition reactions upon the Δ^4 double bond

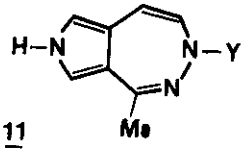
Diazomethane and the highly reactive diazoisopropane add in good yield, site-specifically and regio-specifically, to the Δ^4 double bond of diazepines leading to the corresponding 1-pyrrazolines (40). Pyrolysis of the dimethyl-1-pyrazoline adducts leads to the corresponding homo-diazepines, whereas the acetylated 2-pyrazolines, when treated with a base, give monocyclic pyrazoles via allylic anion intermediates (Scheme 4) (41).

Scheme 4



The synthesis of various homodiazepines is aimed at triggering off an electrocyclic ring transformation leading to an equilibrium with the corresponding bicyclic diaziridines. On the other hand it is hoped that 2-pyrazoline adducts will ultimately permit the synthesis of tetraazaazulenes.

Along similar lines the newly introduced TOSMIC reagent, when reacted with 3-methyldiazepines in the presence of sodium hydride, leads to the corresponding pyrrole derivatives 11, which are potential precursors for triazaazulenes (42).



11

CONCLUSION AND ACKNOWLEDGEMENT

We have shown that 1,2-diazepines, which can be obtained in excellent yield by a specific photochemical process, are versatile synthons for the build-up of more elaborate polyheterocyclic molecules all of which bear new structural features.

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