RESERCH REPORT

CYCLOADDITIONS OF 1,3,4-OXADIAZIN-6-ONES(*) (**)

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Summary — From substituted 2-oxoethanoic acids and acylhydrazines the corresponding hydrazones **1** are prepared, which can be cyclized to give the title compounds **2**. The reactions of **2** with activated alkynes (ynecamines, cyclooctyne, dehydrobenzene) proceed as [4+2]-cycloadditions and result in the formation of α-pyrones after loss of nitrogen. Reactions of this type are possible also intramolecularly, if the oxadiazinones (**2r-u**) contain a properly located alkyne group. Oxadiazinones **2** undergo Diels-Alder cycloadditions with a variety of olefins. Diaryloxadiazinones react with alkenes which are activated by ring strain (cyclopropene, cyclobutene, *trans*-cyclooctene), by a high-lying HOMO (benzvalene, styrene, enamines), or by the factor «x» in the case of norbornene. The methyl phenyloxadiazinonecarboxylate **2p** is highly reactive and takes up even 1-octene and cyclohexene. The primary adducts of type **54** readily extrude nitrogen to give 4,5-dihydropyrylium-2-olates (**60**) as most probable but not observed intermediates. In one case the expected [4+2]-cycloadduct, namely **26**, could be isolated. The ultimate products are generally derived either from **60** or from γ-keto ketenes **53**, which are believed to be in equilibrium with **60**. γ-Keto ketenes **53** have been detected with many systems and are stable in certain cases. When diphenyloxadiazinone, **2a**, was treated with norbornene, norbornadiene, cyclopentene, *trans*-cyclooctene, or styrene, enol lactones of type **63** were isolated, which are considered to be formed from the intermediate dihydropyryliumolates **62** by a suprafacial [1,5]-H shift. Cyclopropenes and cyclobutene transform oxadiazinones **2** to α,β-unsaturated seven-membered enol lactones **64-67** and eight-membered enol lactone **69**, respectively. These products are believed to be the result of valence isomerizations of the corresponding dihydropyryliumolates (**74, 75**). Enamines behave exceptionally in that they can convert the oxadiazinones **2** into products not derived from the [4+2]-cycloaddition (*e.g.* **82, 88, 89**), although the latter process is dominating in most examples investigated to date. The compounds obtained from the usual [4+2]-cycloadditions are amides of α,β-unsaturated δ-oxo acids (**78, 80**) and α,β-unsaturated δ-amino-δ-lactones (**81**). The former are believed to arise from α-amino-γ-keto ketene intermediates (**76**) by [1,3]-amino migrations, whereas the formation of the latter (**81**) can be rationalized in two different ways, one being a [1,5]-amino migration starting from the possible intermediates **85** (4-amino-4,5-dihydropyrylium-2-olates). Cyclobutanone derivatives **50** and **52** and cyclopentanone derivatives **16** originate from γ-keto ketenes generated from *cis,trans*-1,5-cyclooctadiene, *o*-vinylstyrene, and benzvalene, respectively. In these cases, intramolecular cycloaddition of the ketene functionality occurs across either the CC double bond or the strained bicyclo[1.1.0]-butane sigma bond, respectively. Intermolecular [2+2]-cycloadditions of the corresponding γ-keto ketenes with cyclopentadiene, 2,3-dihydrofuran, and cyclooctyne give rise to cyclobutanone derivatives (**34, 38**), and the cyclobutenone derivative **106**. Several stable γ-keto ketenes were subjected to some more reagents: **20p** is converted by gaseous hydrogen chloride into δ-chloro-δ-lactone **98p**, which can easily be transformed into keto ester **95**. δ-Chloro-β-lactones **98b, 99**, and **100** are obtained analogously. Formic acid and acetic acid produce δ-acyloxy-δ-lactones (**101, 102**) from **20p**. Trifluoroacetic acid, however, does not give stable δ-lactones. So far unidentified products are formed instead, which furnish δ-oxoalkanoic acids (**103, 104**, monoester of the bisacid corresponding to **95**) on hydrolysis. The methanolysis of γ-keto ketenes may lead to the corresponding methyl esters (**90, 95**), but other products have also been found, *e.g.* δ-methoxy-δ-lactone **93** and semiacetals of cyclopentane-1,2-dione derivatives (**96, 97**). Remarkably, the latter compounds seem to result in a new variant of the Dieckmann condensation, proceeding under neutral conditions. Norbornene was found to react with **20p** at elevated temperature to give the symmetric lactone **107**. This process is of special interest since it provides good evidence for the dihydropyryliumolate **92p**, which is trapped by norbornene in a Diels-Alder fashion to give the saturated δ-lactone **107**.

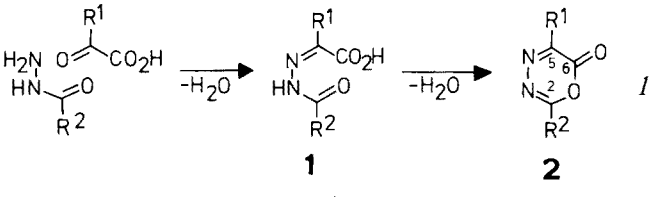
(*) Cycloadditions with 1,3,4-oxadiazin-6-ones (4,5-diaza-α-pyrones), Part V; for Part IV see ref. 7. This *Research Report* is based on a lecture presented at the XI European Colloquium on Heterocyclic Chemistry, Ferrara, October 7-9, 1985.

(**) Dedicated to Professor Siegfried Hünig on the occasion of his 65th birthday.

Although the Diels-Alder reaction was discovered as early as in 1928, it is still most timely to conduct research on this subject. Looking back, one recognizes several stages in the development of the field. At first, the activities were focussed on the preparation of compounds, which we would nowadays designate as simple ones[1a], and secondly, the mechanistic and theoretical aspects became of more importance[1b,c]. In recent years, however, main efforts concentrated on the synthesis of rather complex molecules such as polycyclic compounds, utilizing intramolecular Diels-Alder reactions[1d]. In addition, the search for new types of the Diels-Alder reaction with inverse electron demand is actively pursued at present, the scope and limitations of which have not fully been investigated to date. As part of this subject, the synthetic potential of aza-1,3-dienes acting as dienophiles has been reviewed recently[1e]. This *Research Report* describes the cycloadditions of 1,3,4-oxadiazin-6-ones, a new 2,3-diaza-1,3-diene system, with alkynes and alkenes. Not only unprecedented synthetic strategies are offered by these reactions, but also mechanistic highlights as a consequence of the propensity of the primary Diels-Alder adducts to eliminate molecular nitrogen readily.

1. PREPARATION AND SOME PROPERTIES OF 1,3,4,-OXADIAZIN-6-ONES

The preparation of 2,5-diphenyl-1,3,4-oxadiazin-6-one, **2a**, the first member of this class of heterocycles, has been described by Steglich and coworkers[2]. They found that the treatment of 2-oxo-2-phenylethanoic acid benzoylhydrazone, **1a**, with trifluoroacetic anhydride or dicyclohexylcarbodiimide causes formal elimination of water to furnish the oxadiazinone ring.



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Encouraged by our preliminary results obtained from the reactions of **2a** with several olefins[3a], we have prepared the diaryloxadiazinones **2b-g** *via* the hydrazones **1b-g** starting from the corresponding 2-oxo-2-arylethanoic acids and aroylhydrazines (eq. *1*), and utilizing the dicyclohexylcarbodiimide method in the cyclization step[3b,4]. Steglich and Gansen[5] have also carried out the synthesis of many more diaryloxadiazinones such as **2b,g-l** and several other derivatives with an unsaturated side chain in the *ortho* position of R^2, which undergo intramolecular [4+2]-cycloadditions (see **2s-v** in *Section 2* and **2w** in *Section 3.3*), and 1,4-bisoxadiazinonylbenzene **2q** as well as 1,3,5-trisoxadiazinonylbenzene **2r** (see *Section 2*). In some of these syntheses, it was shown that acetic anhydride, methanesulphonyl chloride, and toluenesulphonyl chloride are also useful cyclization reagents.

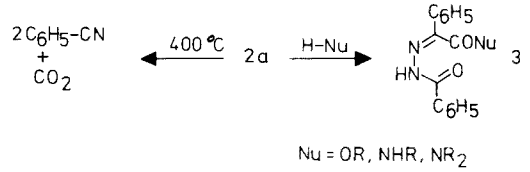
TABLE 1 - FORMATION OF HYDRAZONES **1** AND OXADIAZINONES **2** FROM 2-OXO-2-ARYLETHANOIC ACIDS AND AROYLHYDRAZINES

R^1	R^2	**1**	Yield (%)	**2**	Yield (%)	Ref.
C_6H_5	C_6H_5	**1a**	82	**2a**	79	2
C_6H_5	4-$NO_2C_6H_4$	**1b**	89	**2b**	40,90	4,5
4-$NO_2C_6H_4$	C_6H_5	**1c**	74	**2c**	54	4
C_6H_5	4-$CH_3OC_6H_4$	**1d**	82	**2d**	41	3b,4
4-$CH_3OC_6H_4$	C_6H_5	**1e**	67	**2e**	41	4
4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	**1f**	77	**2f**	62[a]	3b,4
C_6H_5	4-pyridinyl	**1g**	84,100	**2g**	58[a],68	3b,4,5
C_6H_5	4-ClC_6H_4	**1h**	90	**2h**	77	5
C_6H_5	1-naphthyl	**1i**	67	**2i**	100	5
1-naphthyl	C_6H_5	**1j**	100	**2j**	94	5
1-naphthyl	4-ClC_6H_4	**1k**	80	**2k**	70	5
C_6H_5	2-furanyl	**1l**	100	**2l**	89	5
C_6H_5	CH_3	**1m**	63[b]	**2m**	76	6
C_6H_5	$CH_2C_6H_5$	**1n**	66	**2n**	79	6
CH_3	C_6H_5	**1o**	85[b]	**2o**	68	6
C_6H_5	CO_2CH_3	**1p**	90	**2p**	60	7,8a

([a]) Containing some dicyclohexylurea. ([b]) Overall yield *via* the *E* isomer of the hydrazone.

Padwa and Eisenbarth[6] have obtained the first oxadiazinones with an alkyl side chain, *i.e.* the methyl derivatives **2m,o** and the benzyl derivative **2n**. The methyl-substituted (*Z*)-hydrazones **1m,o** required for the cyclization could not be prepared directly but had to be generated from the initially produced (*E*)-hydrazones by treatment with *p*-toluenesulphonic acid or by heating. Methyl 5-phenyloxadiazinone-2-carboxylate, **2p** , has been prepared from 2-oxo-2-phenylethanoic acid and methyl oxalate hydrazide *via* the hydrazone **1p**[7,8a].

Because of UV absorptions at 274-475 nm (log $\varepsilon \approx 4$ in most compounds) the oxadiazinones are coloured substances. On heating to 400 °C, **2a** decomposes to benzonitrile and carbon dioxide[2] (eq. *2*). The lactone functionality of the oxadiazinones is attacked by alcohols (except *tert*-butyl alcohol) and primary and secondary amines to give the acylhydrazones **3** of 2-oxoethanoic acid esters and amides, respectively[5] (eq. *2*). In a mixture of 10 ml of tetrachloromethane and 1 ml of methanol, 0.5 mmol of **2a** had a half-live of about 1 h at 20 °C[4].



2

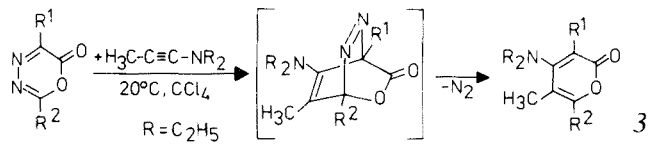
Nu = OR, NHR, NR_2

2. ADDITION OF ACETYLENES TO 1,3,4-OXADIAZIN-6-ONES

The most interesting reactions of oxadiazinones **2** reported by Steglich and coworkers[2,5] are the cycloadditions with acetylenes. A different outcome was encountered depending on what an alkyne, either a stable or a transient one, *i.e.* an aryne, was utilized.

2.1. Stable alkynes

In the case of 1-diethylaminopropyne, the α-pyrones **5a,h,i** (yields 72, 71, 52%, respectively) were formed from **2a,h,i**, probably *via* the Diels-Alder adducts **4**; the latter could not be observed due to the rapid loss of nitrogen (eq. *3*). With two equivalents of the ynamine, the 1,4-bisoxadiazinonylbenzene **2q** gave rise to the 1,4-bis(5-pyronyl) benzene **5q** in 67% yield (eq. *4*).



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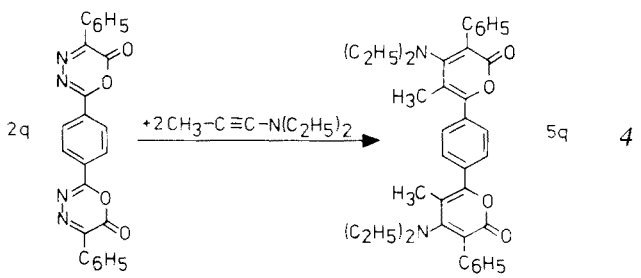

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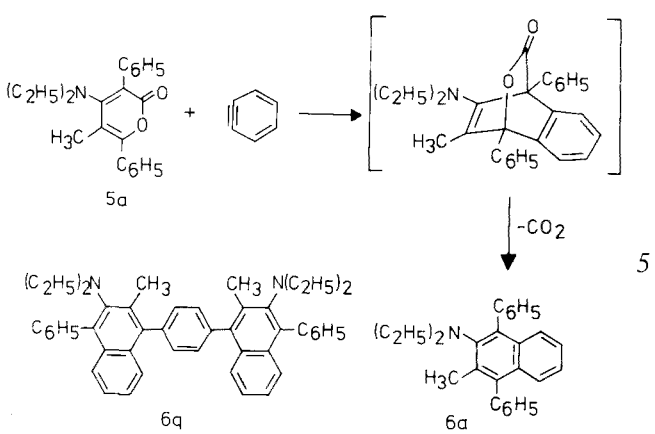
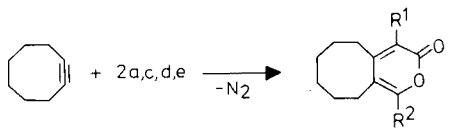
An excess of the ynamine did not attack the α-pyrones **5**; however, the more reactive benzyne underwent the [4+2]-cycloaddition to afford the naphthalene derivatives **6a,q** (yields 42, 19%, respectively) after loss of carbone dioxide[5] (eq. *5*).



5

Sauer and coworkers[9] have carried out rate measurements of the cycloadditions of **2a,c,d,e** with cyclooctyne, which give rise to the α-pyrones **7a,c,d,e** (eq. *6*). Compared to the second-order rate constant of **2a**, those of the *p*-methoxy derivatives **2d,e** are decreased by factors of 0.7 and 0.5, respectively, and that of the *p*-nitro derivative **2c** is increased by a factor of 2.6. The rate constants have been correlated with the reduction potentials of the oxadiazinones.



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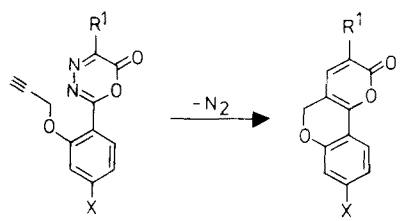
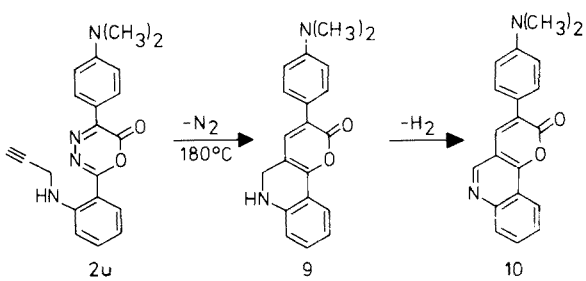
When an oxadiazinone contains a properly located acetylene group, the Diels-Alder additions can take place intramolecularly. Such a process was found to be operative even under the conditions of the synthesis of *o*-propargyloxy-substituted diphenyloxadiazinone **2r**, whereas *p*-dimethylamino-substituted derivatives **2s,t** required heating to about 180 °C. The products were identified to be the chromeno-α-pyrones **8r,s,t,** (yields 95, 67, 72%, respectively)[5] (eq. *7*).



	R¹	X	
2r	C_6H_5	H	8r
2s	4-$N(CH_3)_2C_6H_4$	H	8s
2t	4-$N(CH_3)_2C_6H_4$	Cl	8t

7

The cyclization of the *o*-propargylamino-substituted oxadiazinone **2u** in the same manner gave rise to **9** (87% yield), which was partially dehydrogenated under the reaction conditions to furnish the quinolino-α-pyrone **10**. By bubbling air through the reaction mixture or by adding one equivalent of elemental sulphur, product **10** was also obtained in high yield[5] (eq. *8*).



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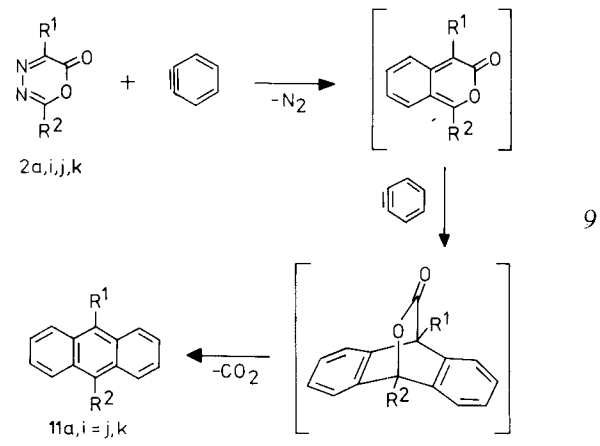
2.2. Arynes

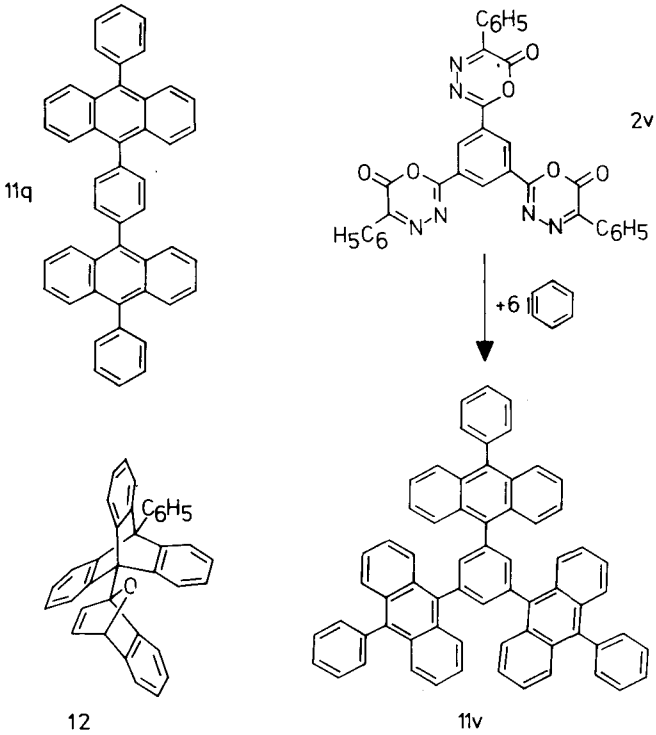
On treatment of the oxadiazinones **2a,i,j,k** with benzyne, the reactions did not stop at the α-pyrone stage but addition of another benzyne molecule ensued leading to the 9,10-diarylanthracenes **11a,i=j,k** (yields 60, 52, 52, 62%, respectively)[2,5] (eq. *9*).



2a,i,j,k 9 11a,i = j,k

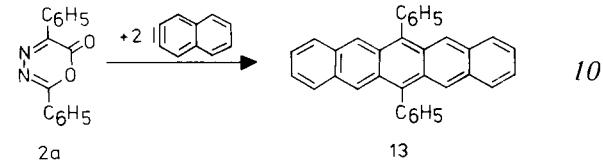
Analogously, bisoxadiazinonylbenzene **2q** and trisoxadiazinonylbenzene **2v** afforded the aromatic hydrocarbons **11q** (40% yield) and **11v** (24% yield), respectively[5] (scheme 1). An excess of benzyne may convert the anthracene derivatives into triptycene derivatives. Thus, triptycene **12** was obtained in 10% yield from the reaction of oxadiazinone **2l** with benzyne[5] (scheme 1).

SCHEME 1



11q 2v 12 11v

The use of 2,3-dehydronaphthalene instead of benzyne leads to the formation of more extended aromatic hydrocarbons. For example, 6,13-diphenylpentacene, **13**, was prepared in 42% yield from oxadiazinone **2a**[5] (eq. *10*).



2a 13 *10*

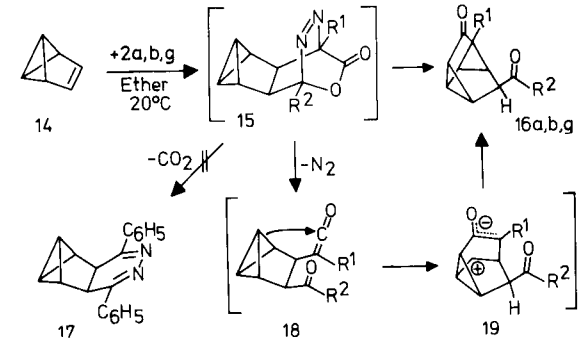
The inter- and intra-molecular additions of diaryloxadiazinones with acetylenes clearly reveal a high potential for the preparation of certain polycyclic α-pyrones and aromatic hydrocarbons, some of which would be tedious to synthesize by other routes.

3. REACTION OF OLEFINS WITH 1,3,4-OXADIAZIN-6-ONES

3.1. Benzvalene

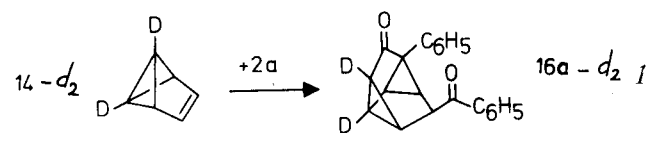
In Diels-Alder additions with inverse electron demand, benzvalene, **14**, had been shown to be a very reactive dienophile[10a,b]. Thus, we considered **14** as a suitable reagent for a [4+2]-cycloaddition reaction with **2a** and expected the formation of dihydropyridazine **17** after the loss of carbon dioxide from the primary adduct **15**. The elimination of carbon dioxide is generally encountered, when Diels-Alder adducts of α-pyrones are heated[10b,c]. Compound **17** had been obtained from the reaction of **14** with 3,6-diphenyl-1,2,4,5-tetrazine, probably *via* an intermediate closely related to **15**[10a]. However, oxadiazinone **2a** failed to transform **14** to **17** and produced the tetracyclic compound **16a** (75% yield) indicating the loss of nitrogen instead of carbon dioxide[3a,4] (scheme 2). Analogously, oxadiazinones **2b,g** gave rise to **16b,g** (yields 79, 75%, respectively)[4].

SCHEME 2



14 15 16a,b,g 17 18 19

Obviously, the Diels-Alder adducts of α-pyrones and their 4,5-diaza derivatives show a fundamentally different behaviour. The following mechanism rationalizes the result. Extrusion of nitrogen from the primary adduct **15** generated the γ-keto ketene **18**. Its electrophilic ketene functionality attacks the bicyclo[1.1.0]butane system, which is known to have nucleophilic properties, and in a formal [2+2]-cycloaddition of the CC double bond with the adjacent cyclopropane bond the cyclopentanone derivative **16** is formed, possibly *via* the zwitterionic intermediate **19** (scheme 2).



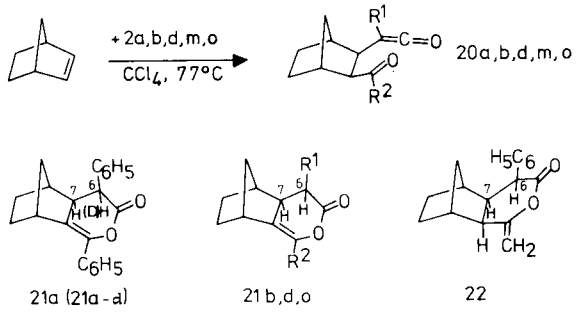
14-d_2 16a-d_2 *11*

This pathway is consistent with the location of the deuterium atoms in the product **16a**-d_2 obtained from oxadiazinone **2a** and dideuteriobenzvalene, **14**-d_2 (eq. *11*). Since the IR spectrum of the reaction mixture did not indicate a ketene intermediate, the intramolecular [2+2]-cycloaddition of **18** must be a very fast process. This was corroborated by carrying out the reaction of **2a** with **14** in the presence of methanol, which can compete neither with **14** for **2a** (*cf.* formation of **3**, Nu = OCH_3) nor with the bicyclobutane moiety for the ketene group of **18**; correspondingly, the yield of **16a** was not diminished[4].

3.2. Norbornene

To support or to discard the mechanism proposed above we reacted oxadiazinone **2a** with norbornene, the σ-system of which should be unreactive towards the ketene functionality in contrast to the bicyclobutane moiety of benzvalene. Because of the lower reactivity of norbornene, the experiment was conducted in boiling tetrachloromethane, and the IR spectrum of the solution displayed a strong absorption at 2100 cm^{-1}, which we assign to the ketene group of γ-keto ketene **20a**. The intensity of this absorption reached a maximum after 7 h, decreased on continued heating and disappeared completely after an additional 3-h heating at 77 °C. Finally, the enol lactone **21a** was isolated in 35% yield[3a,4] (scheme 3).

SCHEME 3

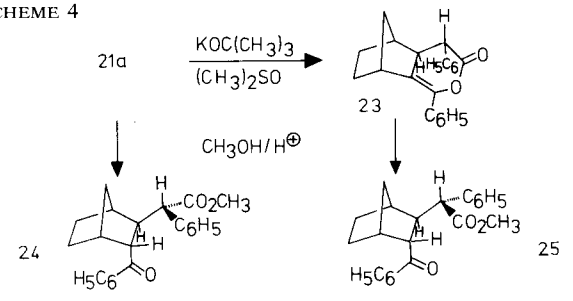


An analogous set of reactions (scheme 3) occurred when oxadiazinones **2b,d,m,o** and norbornene were heated at reflux in tetrachloromethane. Although the cycloadditions took place approximately as fast (reaction time 15-50 h) as that of **2a**, the cyclizations of the γ-keto ketenes proceeded with very different rates. Only after refluxing for two weeks the IR-absorption of the *p*-nitrophenyl derivative **20b** at 2105 cm^{-1} had vanished, and **21b** was isolated in 21% yield [8a]. In contrast, the *p*-methoxyphenyl derivative **20d** could hardly be observed and the enol lactone **21d** (84% yield) was formed almost at the same rate as **2d** was consumed [8c]. Obviously, the rate of the ring closure is determined by the nucleophilicity of the carbonyl group, which has to add to the ketene functionality in **20**. The ketene intermediate **20m** (IR: 2100 cm^{-1}) was formed within 4 h in boiling tetrahydrofuran and had disappeared after 17 h of continued refluxing[8c]. No attempt was made to detect **20o**, but the overall reaction time of 22 h[6] indicates that it cannot be especially long-lived. Interestingly, the isolated products are structurally different. The route to **21o** (63% yield[6]) involves the same type of hydrogen shift as in the formation of **21a,b,d**, whereas in **20m** a hydrogen from the methyl group migrates to give rise to enol lactone **22** (55% yield[8c]) with an exocyclic methylene group.

Unequivocal proof of enol lactone **21a** with the *exo*-phenyl group at C(6) has been derived from a single-crystal X-ray structure analysis[4]. The structures of **21b,d,o** and **22** (scheme 3) are supported by the IR absorption of the carbonyl group (KBr): 1755 (**21a**)[4], 1765 (**21b**)[8a], 1763 (**21d**)[8c], 1760 (**21o**)[6], 1762 cm^{-1} (**22**)[8c]. The magnitude of the H,H-coupling constant $J_{6,7}$ reveals the configuration at C(6) as shown by **21a** (7.0 Hz) and its diastereomer **23** (14.2 Hz)[4]. Since the spectra of **21d** and **22** show values of 7.0 and 7.2 Hz, respectively, the *exo* orientation of the substituents at C(6) is indicated also in these compounds[8c]. We assume the same configuration for **21b,o** (see *Section 3.5*), although the coupling constants $J_{6,7}$ have not been determined.

Recently, Hünig and coworkers[11] reported that certain Diels-Alder additions with inverse electron demand can be accelerated considerably by acid catalysts like trifluoroacetic acid. And indeed, in the presence of $CF_3CO_2H/(CF_3CO)_2O$ the reaction of oxadiazinone **2a** with norbornene proceeded at 40 °C as fast as the uncatalyzed cycloaddition at 77 °C. A ketene intermediate could *not* be observed by means of the IR spectrum of the solution, but the final product was found to be enol lactone **21a** (22% yield). Using deuteriotrifluoroacetic acid we obtained **21a**-*d* with the label selectively incorporated in the *endo*-6-position[4] (scheme 3).

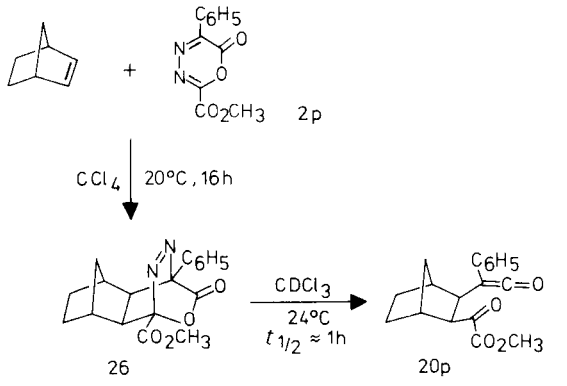
SCHEME 4



The crude product of neither the uncatalyzed nor the catalyzed reaction of oxadiazinone **2a** with norbornene provided any evidence for the formation of **23**, the stereoisomer of **21a**. However, **21a** was converted into **23** (19% yield) by treatment with potas-

sium *tert*-butoxide in dimethyl sulphoxide. The acid-catalyzed methanolysis of **21a** and **23** gave rise to the diastereomeric esters **24** and **25**, respectively, in high yields[4] (scheme 4).

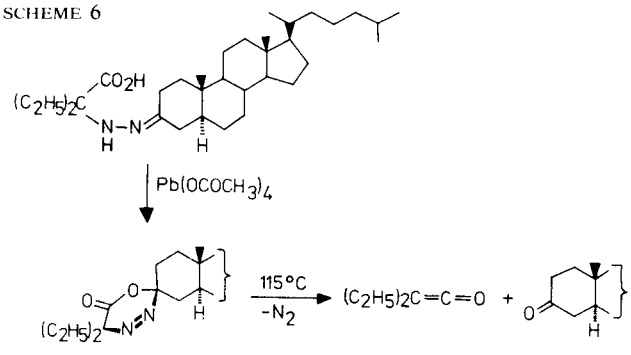
SCHEME 5



Methyl oxadiazinonecarboxylate **2p** turned out to be considerably more reactive than **2a**. The cycloaddition with norbornene (scheme 5) proceeded at a temperature as low as 20 °C. When the reaction was carried out in a quantity of tetrachloromethane insufficient to dissolve **2p** completely, the initially yellow suspension turned into a colourless one within 16 h. The colourless product (isolated in 66% yield) was characterized by analytical and spectral data (UV in hexane: λ_{max} = 376 nm, $\varepsilon \approx 50\ M^{-1}\ cm^{-1}$) and found to be the Diels-Alder adduct **26**. The fortunate circumstance that **26** crystallized rapidly out made its isolation possible; in fact, it lost nitrogen when dissolved in deuteriochloroform with a half-life of about 1 h at 24 °C to give γ-keto ketene **20p**! Even on heating, the latter product did not convert into an enol lactone of type **21**[7].

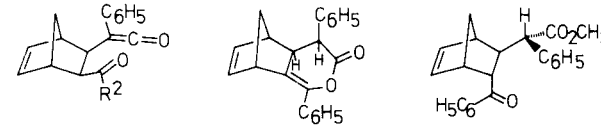
Barton and Willis[12] have prepared a compound containing the heterocyclic unit of **26**. Pyrolysis of this compound at 115 °C smoothly gave diethyl ketene and cholestanone (scheme 6).

SCHEME 6

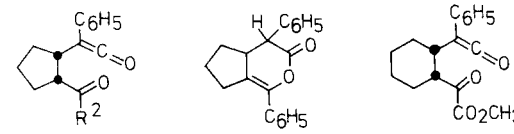


3.3. Norbornadiene, cyclopentene, cyclohexene, cyclopentadiene, *trans*-cyclooctene, 2,3-dihydrofuran, ethyl vinyl ether, 1-octene, 1,3-butadiene, styrene, and allyloxy-substituted oxadiazinone **2w**

Since the progress of most of these cycloaddition reactions was monitored by IR spectroscopy, they were carried out in tetrachloromethane or tetrachloroethane. For example, norbornadiene took up oxadiazinones **2a** (50 °C, 4 days) and **2p** (45 °C, 8 h) to give γ-keto ketenes **27a,p** (IR: 2105, 2100 cm^{-1}). However, primary cycloadducts were not detected. γ-Keto ketene **27a** cyclized to enol lactone **28** (43% yield) on prolonged heating at 45-50 °C, whereas **27p** remained unchanged[8a]. Acid-catalyzed methanolysis of **28** resulted in its conversion into keto ester **29** in high yield[4].

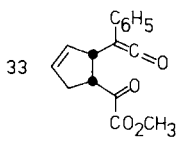


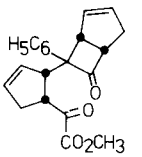
The reaction of diphenyloxadiazinone **2a** with cyclopentene has been found to be very sluggish and only after heating at 100 °C for 10 days, enol lactone **31** was isolated in 4% yield. Addition of trifluoroacetic acid admixed with its anhydride accelerated the process, and after 3 days at 77 °C **31** was obtained in 17% yield. The IR spectra of the reaction mixtures did not provide any evidence for the intermediacy of γ-keto ketene **30a**[4]. In contrast, methyl oxadiazinonecarboxylate **2p** underwent the cycloaddition at 60 °C within 16 h to form the stable γ-keto ketene **30p** (IR: 2100 cm^{-1}). Cyclohexene did not react with **2a**. On the other hand, it added **2p** to give a product with a ketene functionality (IR: 2100 cm^{-1}), probably **32**, when heated at 55 °C for 2 days[8b].



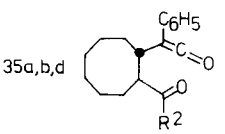
A conclusive result for the reaction of **2a** and cyclopentadiene has not yet been obtained, since the dimerization of cyclopentadiene interfered. Oxadiazinone **2p**, however, produced γ-keto ketene **33** (IR: 2100 cm^{-1}) smoothly (0-20 °C, 14 h), and the latter took up another molecule of cyclopentadiene readily, if this diene was present in excess, to afford a crystalline isomer of cyclobutanone **34** (17% yield, IR in KBr: 1767, 1724 cm^{-1})[8c]. The orientation in the Diels-Alder addition can be derived from the structure of the hydrogen chloride adduct **100** (see *Section 4.2*) of **33**, while the orientation in the [2+2]-cycloaddition was taken to be the usual one encountered in reactions between ketenes and cyclopentadiene[13a]. Since Diels-Alder reactions and [2+2]-cycloadditions of ketenes are governed by *cis*-selec-

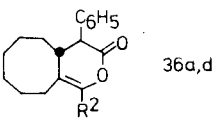
tivity, both the cyclopentene units in **34** should carry *cis*-arranged substituents, but neither the relative configuration of these units nor that of the carbon binding the phenyl group have been established.



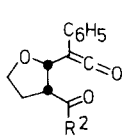


cis-Cyclooctene left **2a** unchanged, whereas the strain energy of *trans*-cyclooctene promoted its cycloaddition strongly. After 3 h at 20 °C, **2a** was consumed quantitatively with formation of γ-keto ketene **35a**[4] and, analogously, **2b,d** generated **35b,d**[8a] (IR: 2090, 2095, 2100 cm^{-1}). On heating to 50 °C, **35a** cyclized with hydrogen migration to form enol lactone **36a** (49% yield), the configuration of which was established unambiguously by means of an X-ray structure analysis[4]. Based on the C=O absorptions in the IR spectra (**36a,d**: 1755 cm^{-1}) **35d** also cyclizes to give an enol lactone (**36d**), but the nitro-substituted γ-keto ketene **35b** seems to refuse to isomerize[8a]. These findings are in accordance with the rates observed for the transformations of the γ-keto ketenes **20a,b,d**, derived from norbornene into enol lactones **21a,b,d**. In the presence of trifluoroacetic acid and its anhydride, at 20 °C oxadiazinone **2a** and *trans*-cyclooctene gave rise to **36a** (16% yield) instantaneously[4].

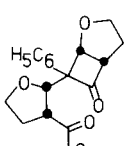




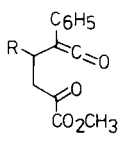
2,3-Dihydrofuran was the first enol ether reacted with the oxadiazinone system[14]. The cycloaddition of **2a** in the boiling dienophile afforded two diastereomers devoid of nitrogen in 54% yield, which have been characterized as cyclobutanones **38a** on the basis of their spectral data. A similar set of products were formed (**38n**, 42% yield) from the reaction of 2,3-dihydrofuran and the 2-benzyl-substituted oxadiazinone **2n**. The results obtained are most simply explained by invoking the loss of nitrogen from the initially formed Diels-Alder adduct to give the γ-keto ketene intermediate **37**, which undergoes a subsequent [2+2]-cycloaddition with another molecule of dihydrofuran (the authors[14] drew the products of the wrong orientation in the [2+2]-cycloaddition[13b]).



37a,n

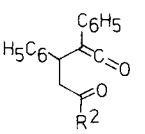


38a,n

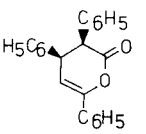


R	C_2H_5O	*n*-C_6H_{13}	C_2H_3
	39	40	41

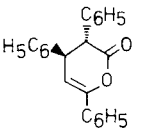
Our attempts to add ethyl vinyl ether, 1-octene, and 1,3-butadiene to diphenyloxadiazinone **2a** were not successful[8a]. The more reactive **2p**, however, caused strong IR absorptions of the reaction mixture at 2110, 2100, and 2100 cm^{-1} on treatment with these olefins at 20, 60 and 20 °C, respectively. Obviously, after the Diels-Alder addition, γ-keto ketenes are produced. Although the regiochemistry in the cycloaddition step has not yet been established, we prefer the orientation leading to **39-41** by analogy with the styrene case (see below). Evidence for the correct location of the hexyl group in **40** derives from the structure of the acid **103** prepared from the γ-keto ketene (see *Section 4.2*)[8b,c].



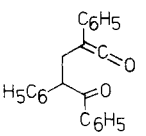
42a,p



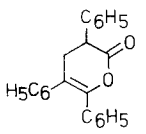
43



44



45



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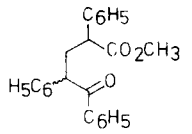
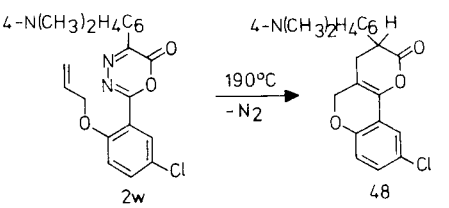


47

For the addition of styrene to **2a**, refluxing in tetrachloroethylene (b.p. 121 °C) was required, and the enol lactones **43, 44**, and **46** were formed in the ratio 2.1:2.1:1.0 (76% total yield). Since the IR spectrum of the reaction mixture displayed an absorption at 2100 cm^{-1}, the intermediacy of the γ-keto ketenes **42a** and **45** is indicated. As estimated from the product ratio, oxadiazinone **2a** prefers one of the two orientations in the cycloaddition with styrene by a factor of four[4]. Oxadiazinone **2p** appears to react more selectively. By ^{1}H-NMR spectroscopy only a single γ-keto ketene has been observed, which was converted into acid **104** (see *Section 4.2*) and thus has the structure **42p**[8b].

Compounds **43** and **44** were identified by comparison with authentic samples[15], whereas enol lactone **46** has been characterized by converting it into two diastereomeric methyl 5-oxo-2,4,5-triphenylpentanoates (**47**) on acid-catalyzed methanolysis. A similar mixture of the isomers **47** have been prepared by an independent route[4].

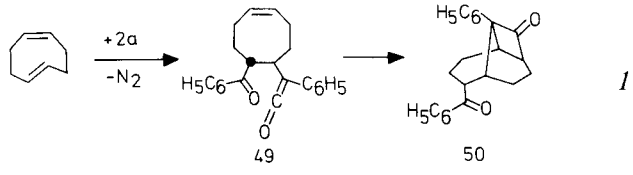


Together with the intramolecular acetylene additions to the diazadiene system of the oxadiazinone nucleus (*cf.* products **8-10**) an analogous olefin addi-

tion has been carried out[5]. Thus, after refluxing the allyloxy-substituted diaryloxadiazinone **2w** in diethylene glycol diethyl ether, enol lactone **48** was isolated in 62% yield. This result shows that the usual course is followed, *i.e.* [4+2]-cycloaddition, [4+2]-cycloreversion with elimination of nitrogen, and hydrogen migration with formation of an enol lactone. However, in the transition state of the Diels-Alder addition, the steric constraints associated with the intramolecular dienophile moiety reverse the preferred regiochemistry observed in the intermolecular addition of a 1-alkene, namely 1-octene, to **2p**.

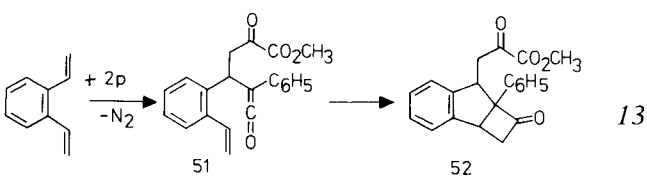
3.4. *cis, trans*-1,5-CYCLOOCTADIENE AND *ortho*-VINYLSTYRENE

In the reaction of benzvalene, **14**, with oxadiazinone **2a**, γ-keto ketene **18**, could not be observed. According to the proposed mechanism, the intramolecular cycloaddition of the ketene functionality to the adjacent bicyclobutane bond must be faster than the initial Diels-Alder addition. A similar intramolecular cycloaddition is conceivable if an oxadiazinone is treated with a diene, and under such a circumstance, the ketene intermediate would have the possibility to form a cyclobutanone moiety in a [2+2]-cycloaddition with the remaining CC double bond. In principle, this would be a procedure for synthesizing cyclobutanone derivatives with at least one anellated ring[16].



49 50 *12*

Our search for suitable dienes was successful in two cases. The highly strained *trans* double bond of *cis,trans*-1,5-cyclooctadiene attacked diphenyloxadiazinone **2a** at 20 °C as shown by the IR spectrum of the reaction mixture. An absorption at 2090 cm^{-1} was observed for a short time, thus indicating the intermediacy of γ-keto ketene **49** (eq. *12*). The work-up after 2 h afforded the tricyclic cyclobutanone derivative **50** in 69% yield, the structure of which was unequivocally proven by an X-ray analysis[4].

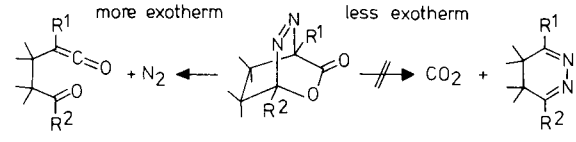


51 52 *13*

o-Vinylstyrene did not affect **2a** but consumed methyl oxadiazinonecarboxylate **2p** in refluxing tetrachloromethane within 7 h (eq. *13*). Again, a transient ketene was detected by IR spectroscopy (2105 cm^{-1}). The isolated product (52% yield) exhibited characteristic IR absorptions at 1782 (cyclobutanone) and 1753 cm^{-1} and in the ^{1}H-NMR spectrum geminal H,H-coupling constants of 17.6 and 19.4 Hz, the magnitude of which is clearly indicative for π-electron systems, *i.e.* a carbonyl group, directly attached to the methylene groups. The latter data suggest structure **52** for the cyclobutanone derivative and rule out the other alternatives. Consequently, the structure of the γ-keto ketene must be **51**, thus supporting an orientation for the Diels-Alder addition of *o*-vinylstyrene, which is consistent with the preferred regiochemistry of the styrene addition to **2a** and **2p** (*cf.* **42a,p**). The configuration of **52** has not yet been established.

3.5. ON THE MECHANISM OF THE NITROGEN ELIMINATION FROM THE DIELS-ALDER ADDUCTS AND THE FORMATION OF THE ENOL LACTONES FROM THE γ-KETO KETENES

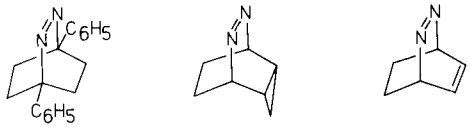
In all the reactions of olefins described above, it is supposed that Diels-Alder adducts of type **54** are formed initially, although only one, namely **26**, could be detected and characterized. Why do these 2-oxa-5,6-diazabicyclo[2.2.2]oct-5-ene-3-ones eliminate nitrogen rather than carbon dioxide to give γ-keto ketenes (**53**) and not 4,5-dihydropyridazines of type **55** (eq. *14*)? The answer is given by a rough estimation using average bond energies, which suggest a larger gain in energy on elimination of nitrogen by almost 40 kcal mol^{-1}. The large bond energy of the N_2-molecule is mainly responsible for this value, and the elimination of nitrogen from the Diels-Alder adducts **4** of oxadiazinones **2** with acetylenes should be driven by the same force, although compounds **4** could loose carbon dioxide as well but do not undergo this type of cycloreversion.



53 54 55 *14*

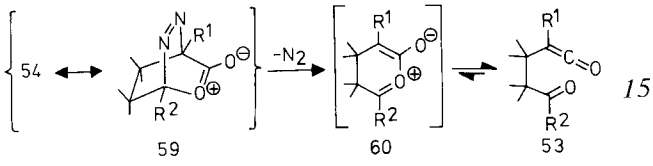
The rationalization of the preference for the nitrogen extrusion raises another question immediately. Why does the decomposition of **54** take place so fast, *i.e.* at or below room temperature? Azo compound **56** clearly shows that phenyl groups attached to the bridgehead positions of **54** cannot surely be responsible for the lability of **54**, since the thermolysis of **56** requires a free energy of activation, $\Delta G^{\ddagger}$, of 30 kcal mol^{-1} at 120 °C[17]. The cyclopropane moiety in **57** (*anti*-anellated with respect to the azo group) accelerates the elimination of nitrogen considerably as shown by $\Delta G^{\ddagger}$ = 21 kcal mol^{-1} at 25 °C[18]. Here, the Walsh orbitals of the three-membered ring interact with the CN bonds, and the CC double bonds

of the product (1,4-cycloheptadiene) are partially formed already in the transition state, thus facilitating the elimination of nitrogen in terms of a homo-Diels-Alder cycloreversion. This trend continues in diazabicyclooctadiene **58**, which is not known[19] since the breaking of the CN bonds is part of a Diels-Alder cycloreversion process requiring only very little activation.



56 57 58

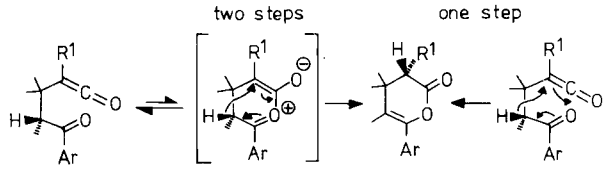
The behaviour of **58** offers the key for an explanation of the thermal instability of oxadiazabicyclooctenones **54**. In ester groups, the formal CO single bond possesses some double bond character causing a rotational barrier of *ca.* 10 kcal mol.$^{-1}$ [20]. Since azo compound **56** generates a highly energetic diradical on elimination of nitrogen, the former is found to be rather stable; by way of contrast, compounds **54** fulfil the requirements for a Diels-Alder cycloreversion because of the partial double bond between the endocyclic oxygen and the carbonyl carbon (as depicted by the resonance structure **59**) and, therefore, decompose rapidly to initially form the 4,5-dihydropyrylium-2-olate derivatives **60**. The latter will readily undergo ring opening to γ-keto ketene **53**. Although intermediates of type **60** escaped direct observation, several reactions of **53** are best understood by invoking a mobile equilibrium between **53** and **60** (see below in this section and *Section 4*, especially the trapping product **107**), the latter being present only in minute quantities (eq. *15*).



59 60 53 *15*

The products isolated from the reaction of diaryl- and methylphenyl-oxadiazinones with olefins discussed above are enol lactones, *viz.* **21, 22, 28, 31, 36, 43, 44** and **46**. In the case of **21a** and **36a** it has been established by X-ray analysis that the hydrogen migration starting from the corresponding γ-keto ketenes takes place suprafacially. The same stereochemical course is followed in several other cases as indicated by NMR data. No information regarding the stereochemistry is available in the remaining cases. Interestingly, in the γ-keto ketene **42a** generated from **2a** and styrene, the two hydrogen atoms of the methylene group could undergo the migration, and, indeed, two products (**43** and **44**) are formed. Thus, none of the results bear any evidence against a suprafacial process. That the hydrogen shift under consideration is a kinetically controlled process is demonstrated by the base-catalyzed isomerization **21a** → **23**. Obviously, the thermodynamically less stable isomer, namely **21a**, is generated on thermolysis of γ-keto ketene **20a**.

Two mechanistic possibilities can be put forward to explain the stereochemical outcome (eq. *16*). The first one, a two-step process, involves ring closure of the γ-keto ketene **61** to 4,5-dihydropyrylium-2-olate **62** and subsequent symmetry-allowed suprafacial [1,5]-H migration. Alternatively, in the one-step process, ring closure and hydrogen shift would occur simultaneously, and this route can be envisaged as intramolecular ene reaction.



61 62 63 61 *16*

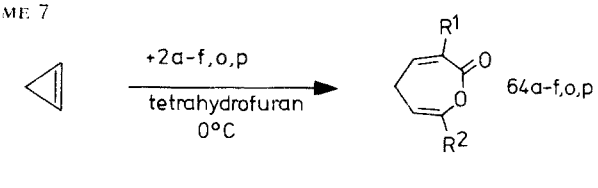
Enol lactones of type **63** are obtained only if an aryl group is attached to the carbonyl group of the γ-keto ketene as in **61**. Replacement of the aryl by a methyl group leads to the migration of a methyl hydrogen with formation of enol lactone **22** having an exocyclic methylene group. If the aryl group in **61** is *p*-nitrophenyl (*cf.* **20b, 35b**), the isomerization to the enol lactone is slowed down or even prevented. The latter is true especially for the γ-keto ketenes with a methoxycarbonyl group instead of an aryl in **61**. These results, however, do not favour one of the above mechanistic alternatives over the other, since the nucleophilicity of the carbonyl oxygen adding to the ketene functionality would play its role on both routes. Furthermore, the trapping product **107** (see *Section 4.3*) demonstrates that γ-keto ketene **20p** is in equilibrium with a 4,5-dihydropyrylium-2-olate, *i.e.* **92p**, in spite of the methoxycarbonyl group. Why, then, the hydrogen shift is prevented remains to be investigated.

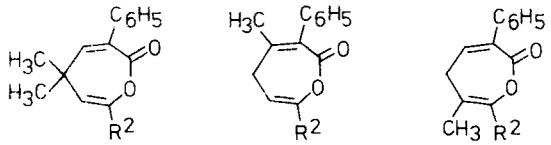
3.6. Cyclopropenes and Cyclobutene

The reactions of these olefins with oxadiazinones **2** follow a route different from that described in *Sections 3.1-3.4*. In fact, the products are enol lactones as well, but a hydrogen shift is not involved in their formation.

For example (see scheme 7), bubbling of unsubstituted cyclopropene through a solution of **2a-f,o,p**, in tetrahydrofuran at 0 °C afforded the oxepinone derivatives **64a-f,o,p** in 86, 59, 70, 71, 79, 53[4], 80[8c], and 97%[8a] yields, respectively. 3,3-Dimethylcyclopropene turned out to be much less reactive, since the addition to **2a,g** required heating to 110-120 °C, and the yields of **65a,g** (10 and 20%, respectively)

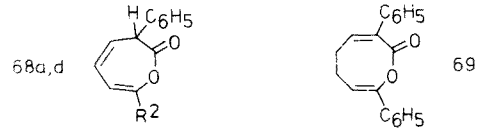
SCHEME 7





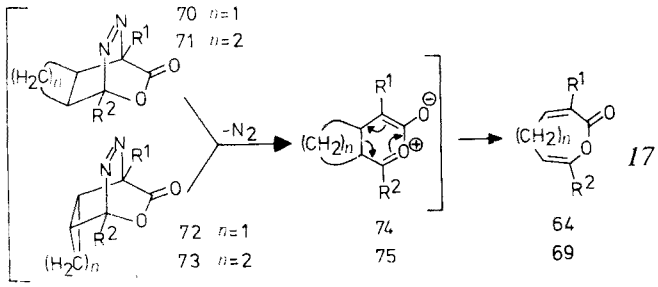
65a,g 66a,p 67a,p

were rather low[4]. Oxadiazinones **2a,p** used up 1-methylcyclopropene at 20 °C and gave rise to mixtures of regioisomers **66a,p** and **67a,p** in 65[4] and 52%[8b] yields, respectively. As already encountered in the styrene additions, **2a** and **2p** display a different regioselectivity, the ratios **66a:67a** and **66p:67p** being 2:3[4] and 4:1[8b], respectively. On treatment with basic alumina, **64a,d** underwent a [1,3]-H shift to furnish the β,γ-unsaturated enol lactones **68a,d**[4]. From the reaction of cyclobutene and **2a** at 110 °C we obtained the α,β-unsaturated eight-membered enol lactone **69** in 26% yield.



68a,d 69

In the reactions of cyclopropene and cyclobutene, intermediates have not been observed. In spite of that, a Diels-Alder addition as the initial step should be postulated which could lead to a mixture of two azo compounds in each case[21], *i.e.* **70, 72** and **71, 73**, if one considers the similar steric demands of the azo and the lactone bridge in the oxadiazinones **2**. This assumption explains the sluggish reaction of 3,3-dimethylcyclopropene, since the close approach of the diene to the dienophile in the transition state is sterically hindered due to the presence of the methyl groups.



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Nitrogen extrusion (as discussed in *Section 3.5*) would convert **70, 72** and **71, 73** into the oxanorcaradiene derivative **74** and the oxabicyclo[4.2.0]octadiene derivative **75**, respectively, the valence isomerization of which would lead to the isolated products **64** and **69** (eq. *17*). The corresponding hydrocarbons undergo the electrocylic ring expansions under very mild conditions: for norcaradiene, $\Delta G^{\ddagger}$ = 6.1 kcal mol^{-1} at −173 °C[22]; for bicyclo[4.2.0]octa-2,4-diene, $\Delta H^{\ddagger}$ = 25.5 kcal mol^{-1} [23].

Because of the stereochemical analogy between azocycloalkane **57** and the primary adduct **72** a direct pathway to **64** in terms of a homo-Diels-Alder cycloreversion would also require only little activation and could therefore compete. Such a route would not be available for **70**, since the stereoisomer of **57** decomposes only above 200 °C ($\Delta H^{\ddagger}$ = 45.9 kcal mol^{-1} [17]). On the basis of the same reaction of the 2,3-diazabicyclo[2.2.2]oct-2-ene derivative with a cyclobutane unit anellated *anti* with respect to the azo group (E_A = 39.2 kcal mol^{-1} [24]), the direct transformation **73** → **69** does not seem to be of importance.

In principle, the intermediates of type **74, 75** could cleave the heterocycle and give rise to γ-keto ketene derivatives; subsequent hetero-Cope rearrangements would furnish the products **64, 69**, respectively. At variance with the discussion in our preliminary communication[3b], we no longer favour this alternative, although retro-Claisen rearrangements of this type would be expected to proceed equally fast[25].

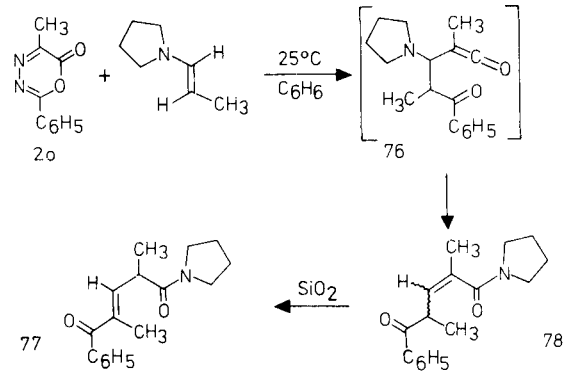
The fact that products of different type form in the cycloadditions of cyclopropene and cyclobutene on one hand and cyclopentene on the other (see *Section 3.3*) are most simply rationalized in terms of ring strain. The opening of the three-membered ring in **74** and the four-membered ring in **75** release strain energies of approximately 28 and 26 kcal mol^{-1}, respectively, whereas the corresponding value for a cyclopentane moiety is about 20 kcal mol^{-1} smaller and, therefore, does no longer provide the driving force. Hence, the 4,5-dihydropyrylium-2-olates generated from cyclopentene are converted into the six-membered enol lactone **31** in the diphenyl case and into the stable γ-keto ketene **30p** in the methoxycarbonylphenyl case.

3.7. Enamines[14,26]

With respect to the reactions with oxadiazinones **2**, enamines show an exceptional behaviour. In fact, the cycloaddition and subsequent nitrogen extrusion encountered with other olefins may occur; they are however dependent on the nature of the enamine and the oxadiazinone, since Padwa and Eisenbarth[14,26] also isolated compound resulting from other pathways. In many reactions, amides of type **3** (Nu = NR_2) were found as side products, since the secondary amine present in the enamine as impurity or liberated by the interaction of the enamine with **2** in a multi-step process opens the oxadiazinone ring instantaneously.

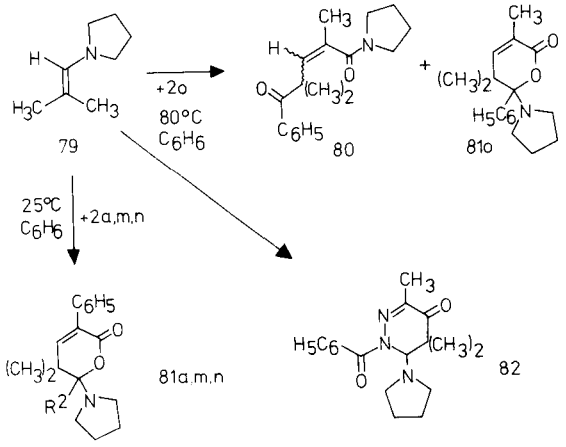
Thus, at 20 °C in benzene (scheme 8), oxadiazinone **2o** and (*E*)-1-propenylpyrrolidine afforded the α,β-unsaturated amides **78** (mixture of *E* and *Z* isomers),

SCHEME 8



which rearranged to the β,γ-unsaturated isomer **77** (49% yield) when chromatographed on silica gel. The formation of **78** can be rationalized in terms of the intermediacy of γ-keto ketene **76** produced upon elimination of nitrogen from the corresponding primary cycloadduct. In order to give rise to **78** the pyrrolidino group in **76** must formally undergo a [1,3]-shift probably *via* a four-membered ring intermediate. The reaction pattern thus deviates from that of γ-keto ketenes of type **61**, which afford six-membered enol lactones.

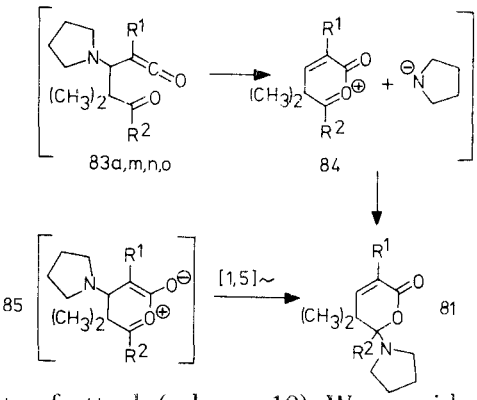
SCHEME 9



When oxadiazinone **2o** was made to react with 1-(2-methylpropenyl)pyrrolidine, **79**, at 80 °C in benzene (scheme 9), four products [**80** (*E* and *Z* isomer), **81o**, and **82**] formed in the ratio 4.0:3.3:2.8:1.0 which were isolated by chromatography. Compounds **81a,m,n** (yields 60, 54, 80%, respectively) were obtained as major products from the reaction of **79** and **2a,m,n**. The pathway to the α,β-unsaturated amide **80** should be the same as that for **78** in the previous reaction and should involve γ-keto ketene **83o**. The intermediates **83** are supposed to serve also as precursors for the α,β-unsaturated lactones **81** (scheme 9).

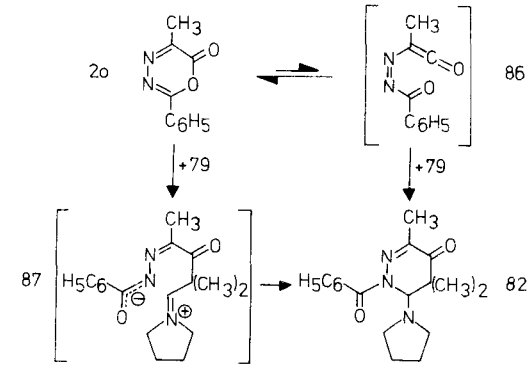
Padwa and Eisenbarth[14] assumed that the ring closure of **83** is followed by pyrrolidine anion ejection to give intermediate **84**. This ion pair then would collapse to produce either **81** or **80** depending on

SCHEME 10



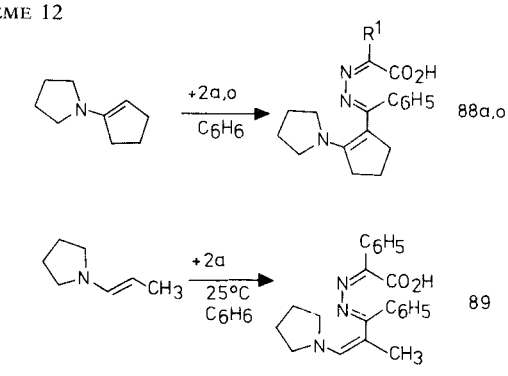
the site of attack (scheme 10). We consider the ion pair **84** as a species of too high an energy to be of importance and prefer the route *via* 4,5-dihydropyrylium-2-olate **85**, which should be the precursor of **83** as discussed in *Section 3.5*. In **85** the pyrrolidinyl group would have to undergo a [1,5]-migration, and this process would be closely related to the formation of the enol lactones **63**.

SCHEME 11



The authors[14,26] rationalized the formation of product **82**, which has not lost nitrogen, in terms of an electrocyclic opening of **2o** to the ketene derivative **86** and subsequent Diels-Alder reaction of this diazadiene with the added enamine **79**. Since further evidence for intermediate **86** is lacking, we propose that enamine **79** attacks the carbonyl group of **2o** to give zwitterion **87**, the collapse of which would be a straightforward route to **82** (scheme 11).

SCHEME 12



Still another pathway (scheme 12) is followed when oxadiazinones **2a,o** are treated with 1-pyrrolidinocyclopentene in benzene at 25 and 85 °C, respectively. The diazatriene **88a** was isolated in 77% yield. Its formation can be explained by attack of the enamine β-carbon to the 2-position of **2a** and a subsequent hydrogen shift from the former enamine β-carbon to the carbonyl oxygen. Heating of **88a** in wet benzene afforded 3-phenyl-1,4,5,6-tetrahydrocyclopentapyrazole and benzaldehyde. This process can be envisaged as proceeding *via* an initial decarboxylation, subsequent hydrolysis, cyclization, and pyrrolidine elimination. The same pyrazole was obtained in 72% yield when oxadiazinone **2o** and 1-pyrrolidinocyclopentene were heated in refluxing benzene. Compound **88o** is believed to be the intermediate. Analogously, **2a** and (*E*)-1-propenylpyrrolidine gave rise to 4-methyl-3-phenylpyrazole and benzaldehyde *via* the isolable diazatriene **89**.

3.8. The Reactivity of Olefins towards 1,3,4-Oxadiazin-6-ones and the Regioselectivity of These Additions

In table 2 conditions and yields of the cycloadditions of olefins with oxadiazinones **2a** and **2p** are collected together with the first ionization potentials (1st IP) of the olefins and the decrease of strain energy on conversion of a cycloalkene or a cycloalkadiene into the corresponding cycloalkane or cycloalkene, respectively. All the olefins listed are nucleophilic. An attempt to react maleic anhydride, an electrophilic dienophile, with **2a** was not successful. All the cycloadditions of **2p** occur under milder conditions than the corresponding ones of **2a**. Thus, the reactions are accelerated by the better electron-withdrawing ability of the methoxycarbonyl group of **2p** relative to that of the phenyl group of **2a**. These facts clearly characterize the Diels-Alder additions of oxadiazinones **2** as those with inverse electron demand[1c]. The difference of reactivity between **2a** and **2p** is qualitatively in accordance with the expectation based on the rate measurements for the additions of cyclooctyne to 3,6-diphenyl-1,2,4,5-tetrazine and dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate[9].

Styrene and 1-(2-methylpropenyl)pyrrolidine are the only open chain olefins which attack **2a**. Presumably, their reactivity is caused by high energy HOMOs as indicated by their first ionization potentials. On the basis of those parameters, 1-octene, 1,3-butadiene, and ethyl vinyl ether are strongly disfavoured. Operating at temperatures higher than those employed in the reaction of styrene to achieve the cycloaddition of these olefins is of no use in view of the thermal decomposition of **2a** (see *Section 1*), whereas the application of high pressure should be helpful[1c]. Since a good yield was obtained in the styrene addition to **2a**, the complete failure of **2a** to react with *o*-vinylstyrene is not easy to rationalize. Most likely, the low concentration of this dienophile in that experiment was responsible for the failure.

In the case of cycloolefins, the relief of strain seems to provide a major part of the driving force and should also control the height of the activation barrier, since part of the strain energy is released already in the transition state. In addition to this, the high energy of the HOMOs should promote the reactivity of benzvalene, *trans*-cyclooctene, and *cis*, *trans*-1,5-cyclooctadiene considerably.

The olefins in table 2 labelled with "no reaction" towards oxadiazinone **2a** smoothly give a γ-keto ketene with **2p**, but not in all cases crystalline products have been obtained therefrom to date. Further, some of the isolated yields are poor, but no attempts have been made to optimize the conditions of these preliminary studies. Another reason may be that only crystalline products were collected and stereoisomers possibly formed may have remained undetected in the mother liquor. Investigations aimed at obtaining more complete results are in progress.

Two orientations are possible when unsymmetrically substituted olefins react with oxadiazinones **2**. The results described show that all the olefinic substituents concerned (alkyl, vinyl, phenyl, alkoxy, dialkylamino) direct the β-carbon preferentially towards the 2-position of oxadiazinone **2a**, the only exception being the methyl group of 1-methylcyclopropene, and this preference seems to be enhanced in the cycloadditions of **2p**. In terms of the frontier orbital approximation[1c], the $HOMO_{olefin}$-$LUMO_{oxadiazinone}$ interaction should be the dominating one. Since the HOMOs of all monosubstituted ethylenes have the larger coefficient at the β-carbon[1c], the regiochemistry observed indicates that, in the oxadiazinone LUMO, C(2) has a larger coefficient than C(5), and the difference in **2p** is more pronounced than in **2a**.

4. Reactions of the System γ-Keto Ketene/4,5-Dihydropyrylium-2-olate

4.1. Reactions with Methanol

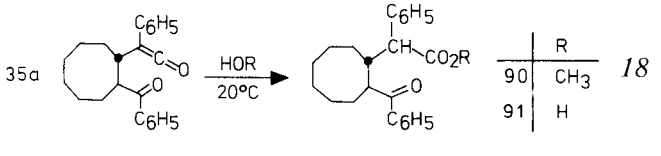
In order to transform γ-keto ketenes into derivatives, which are easier to handle, we considered the addition of methanol as an obvious reaction and expected the formation of substituted methyl 5-oxopentanoates. As already mentioned in *Section 3.1*, methanol cannot trap the transient γ-keto ketene **18** generated from benzvalene and **2a**. Reaction of *trans*-cyclooctene with **2a** gave rise to the rather stable γ-keto ketene **35a** at 20 °C. When this reaction was carried out in the presence of methanol, a methyl

TABLE 2 - INTERRELATION BETWEEN STRAIN ENERGY, FIRST IONIZATION POTENTIAL (1st IP), REACTION CONDITIONS, AND YIELDS FOR THE [4+2]-CYCLOADDITION OF OLEFINS TO 2,5-DIPHENYL-1,3,4-OXADIAZIN-6-ONE, **2a**, AND METHYL 5-PHENYL-1,3,4-OXADIAZIN-6-ONE-2-CARBOXYLATE, **2p**

Olefin	SE[a]	1st IP	Additions of **2a**				Additions of **2p**			
	(kcal mol^{-1})	(eV)	T,°C	t,h	Yield (%)	Products	T,°C	t,h	Yield (%)	Products
Cyclopropene	26.1	9.82[b]	0	fast	86	**64a**	0	fast	97	**64p**
1-Methylcyclopropene			20	fast	65	**66a,67a**	0	fast	52	**66p,67p**
3,3-Dimethyl-cyclopropene		9.42[c]	110	120	10	**65a**				
Cyclobutene	3.6	9.59[b]	110	72	26	**69**				
Cyclopentene	−0.4	9.18[d]	100	240	4	**31**	60	16	34	**99**
Cyclopentadiene	0.1	8.58[e]	result ambiguous				20	14	32	**100**
Norbornene	6.6[f]	8.97[g]	77	10	35	**21a**	20	16	66	**26**
Norbornadiene	7.5[f]	8.69[g]	50	96	43	**28**	45	8	16	**97**
Benzvalene	<10.0[h]	8.55[b]	20	24	75	**16a**				
Cyclohexene	1.4	9.12[d]	no reaction				55	48	*i*	*i*
trans-Cyclooctene	5.4	8.69[j]	20	1	67	**90**				
cis,trans-1,5--Cyclooctadiene	≈17[k]	8.7[k]	20	2	69	**50**				
2,3-Dihydrofuran	−1.2		55	6	62	**38a**				
Ethyl vinyl ether	—	9.15[l]	result ambiguous				20	90	*i*	*i*
1-(2-Methylpro-penyl)pyrrolidine	—	7.66[m]	25	4	60	**81a**				
1-Octene	—	9.60[n]	no reaction				60	48	small	**103**
1,3-Butadiene	—	9.06[o]	no reaction				20	24	*i*	*i*
Styrene	—	8.48[p]	120	24	76	**43,44,46**	50	17	38	**104**
o-Vinylstyrene	—		no reaction				77	7	52	**52**

([a]) Decrease of strain energy (SE) on conversion of a cycloalkene or a cycloalkadiene into the corresponding cycloalkane and cycloalkene, respectively, taken from S.W. BENSON, «Thermochemical kinetics», 2nd ed., John Wiley & Sons, New York, London, Sydney, Toronto, 1976, p. 273, if not otherwise indicated. ([b]) R. GLEITER, *Top. Curr. Chem., 86*, 197 (1979). ([c]) V.V. PLEMENKOV, M.M. LATYPOVA, I.G. BOLESOV, V.V. REDCHENKO, N. VILLEM, J. VILLEM, *Zh. Org. Khim., 18*, 1888 (1982); *J. Org. Chem. USSR, Engl. Transl., 18*, 1651 (1982). ([d]) P. BISCHOF, E. HEILBRONNER, *Helv. Chim. Acta, 53*, 1677 (1970). ([e]) A.D. BAKER, D. BETTERIDGE, N.R. KEMP, R.E. KIRBY, *Anal. Chem., 42*, 1064 (1970). ([f]) A. GREENBERG, J.F. LIEBMAN, «Strained organic molecules», Academic Press, New York, San Francisco, London, 1978, pp. 72 and 94. ([g]) P. BISCHOF, J.A. HASHMALL, E. HEILBRONNER, V. HORNUNG, *Helv. Chim. Acta, 52*, 1745 (1969). ([h]) Estimated from data given by M. CHRISTL, *Angew. Chem., 93*, 515 (1981); *Angew. Chem., Int. Ed., 20*, 529 (1981). ([i]) Preliminary experiments, from which a product has not been isolated so far. The reaction was indicated by the appearence of a strong IR absorption at 2100 cm^{-1}. ([j]) C. BATICH, O. ERMER, E. HEILBRONNER, J.R. WISEMAN, *Angew. Chem. 85*, 302 (1973); *Angew. Chem., Int. Ed., 12*, 312 (1973). ([k]) H.-D. MARTIN, M. KUNZE, H.-D. BECKHAUS, R. WALSH, R. GLEITER, *Tetrahedron Lett.*, 3069, (1979). ([l]) H. FRIEGE, M. KLESSINGER, *J. Chem. Res. (S)*, 208, (1977). ([m]) F.P. COLONNA, G. DISTEFANO, S. PIGNATARO, G. PITACCO, E. VALENTIN, *J. Chem. Soc., Faraday Trans. 2*, 1572 (1975). ([n]) D.A. KRAUSE, J.W. TAYLOR, R.F. FENSKE, *J. Am. Chem. Soc., 100*, 718 (1978). ([o]) C.R. BRUNDLE, M.B. ROBIN, *J. Am. Chem. Soc., 92*, 5550 (1970). ([p]) J.W. RABALAIS, R.I. COLTON, *J. Electron. Spectrosc. Relat. Phenomena, 1*, 83 (1972).

ester **90** with unknown configuration in the side chain was isolated in 67% yield[4]. As expected, the initially formed **35a** was intercepted by methanol instantaneously. The base-promoted hydrolysis of **90** afforded acid **91**, which was also obtained on addition of water to **35a** (eq. *18*).



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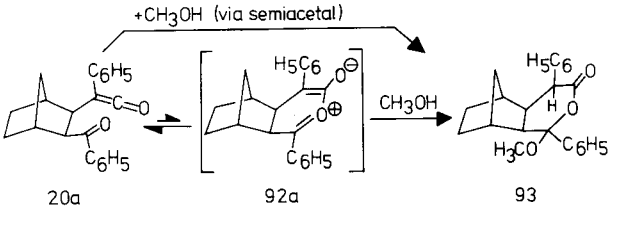
In contrast, the treatment of γ-keto ketene **20a** with methanol did not lead to the expected ester. Since oxadiazinone **2a** is too sensitive to methanol at elevated temperatures (see *Section 1*) the cycloaddition with norbornene could not be conducted in the presence of methanol. Therefore, methanol was added to the reaction mixture after the intensity of the IR absorption of the ketene had reached the maximum. A crystalline 4:1 mixture of the semiacetal lactone **93** and enol lactone **21a** was isolated in low yield[4]. To rationalize this result we assume that methanol undergoes a 1,4-addition to the diene system of 4,5-dihydropyrylium-2-olate **92a**. Alternatively, the nucleophilic attack of methanol could occur at the benzoyl group of **20a**, and in the resulting semiacetal, the hydroxy group would intramolecularly add to the ketene functionality (eq. *19*).



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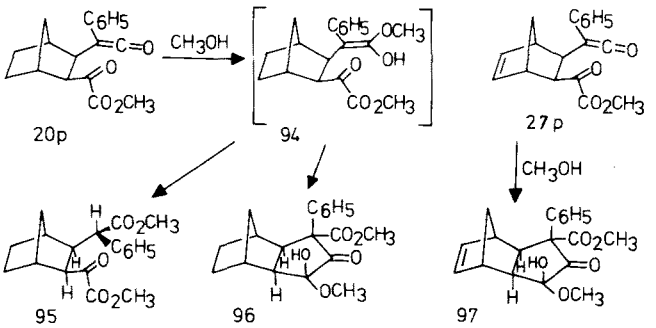
Another unexpected result came from the methanolysis of γ-keto ketene **20p**. The ^{1}H-NMR spectrum of the crude product indicated the presence of six compounds in significant amounts in the ratio 4.2:2.6:2.0:1.4:1.3:1.0 on the basis of twelve methoxy singlets. Only two components of this mixture have been identified so far. The one contributing 1.3 parts to the mixture turned out to be the bisester **95** by comparison of its NMR signals with those of the authentic substance (see *Section 4.2*). The component present in 2.6 parts was isolated in 17% yield by crystallization. An X-ray analysis established the surprising structure **96**, which is a semiacetal of a cyclopentane-1,2-dione derivative[7].

SCHEME 13

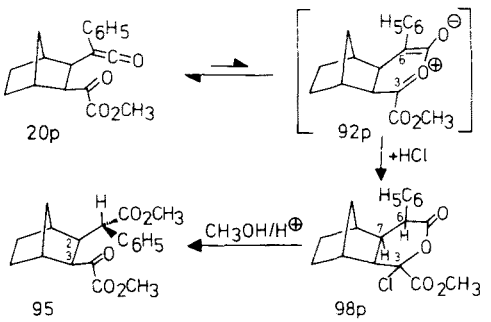


It is assumed (scheme 13) that methanol converts **20p** initially into the enol ester **94**, which either tautomerizes to produce the bisester **95** or undergoes a Dieckmann condensation to give an α-diketone. The latter would have to add one molecule of methanol to generate the semiacetal **96**. Whereas for the normal Dieckmann condensation strongly alkaline conditions are required, the present cyclization to **96** proceeds at a neutral pH. The remaining four compounds of the above mixture could be stereoisomers of **95** and **96** as well as semiacetal lactones of type **93**. Under identical conditions γ-keto ketene **27p** afforded a 16% yield of semiacetal **97**[8a] (scheme 13).

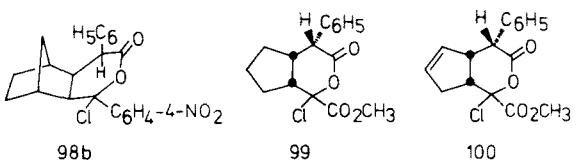
4.2 Reactions with acids

An accidental observation caused the investigation of the behaviour of the γ-keto ketenes towards treatment with acids. Experiments devised to transform **20p** to an enol lactone of type **63** by boiling in polychlorinated solvents were not successful, but small amounts of the chlorolactone **98p** were isolated. It was speculated that the hydrogen chloride formed from cleavage of the solvent had added to the substrate. Thus, bubbling anhydrous hydrogen chloride through the yellow solution of **20p** at 20 °C led to the decolourization of the solution within a few minutes, and **98p** was obtained in 90% yield (IR: 1757, 1780 cm^{-1})[7]. The phenyl group at C(6) occupies the *exo* position as indicated by $J_{6,7}$ = 8.4 Hz, but the configuration at C(3) is not known. A possible explanation of this result involves transfer of a proton from the sterically least hindered side to C(6) of 4,5-dihydropyrylium-2-olate **92p**, which is believed to be in equilibrium with **20p**. In the second step the highly electrophilic C(3) would accept the chloride ion (scheme 14).

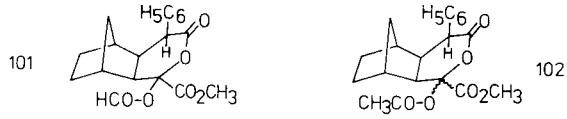
SCHEME 14



The chlorolactones **98b**, **99**, and **100** (yields 15, 34, and 32%, respectively; spectral data very similar to those of **98p**)[8c] were obtained similarly from the γ-keto ketenes **20b**, **30p**, and **33**, respectively.

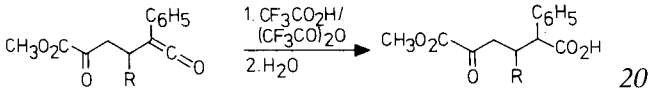


δ-Chloro-δ-lactones are known[27] and can be prepared by treatment of the corresponding 5-oxoalkanoic acids with thionyl chloride. However, compounds of type **98–100** would not be accessible on a conventional route with the same ease as from oxadiazinones **2**. Possessing three functional groups, the chlorolactones prepared from oxadiazinone **2p** *e.g.* **98p**, **99**, and **100**, could be of synthetic importance. For example, acid-catalyzed methanolysis of **98p** gave the bisester **95** in 83% yield[7]. The *exo*, *cis* arrangement of the substituents at the norbornane system of **95** follows from $J_{2,3}$ = 9.2 Hz, whereas the configuration of the methyl phenylacetate moiety should not have changed from that in **98p**. It is of special interest to point out that starting from norbornene and **2p**, one obtaines a product with three newly-created stereogenic centres with effective control of their configurations in high chemical yield.



101 102

In addition to hydrogen chloride, the reactions of other acids were also tried with γ-keto ketene **20p**. For example, formic acid gave rise to formate **101** in 57% yield at 60 °C within 1 h, whereas acetic acid required 3 h at 60 °C to afford a 1:1 mixture of the diastereomeric acetates **102** in 52% yield[8c]. The question whether or not trifluoroacetic acid brings about a product of the same kind has not yet been settled. However, treatment of **20p** with 0.5 equivalents of a mixture of trifluoroacetic acid and its anhydride led to a compound very sensitive to hydrolysis. The isolated product turned out to be an acid, which was converted into bisester **95** by means of diazomethane[8b].

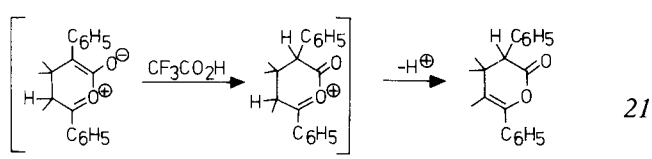


20

40 R = *n*-C_6H_{13} 103
42p R = C_6H_5 104

An analogous set of reactions (eq. *20*) occured when the γ-keto ketenes **40** and **42p** (prepared by addition of 1-octene and styrene, respectively, to **2p**) were treated with trifluoroacetic acid and its anhydride. The configurations of the acids **103** (low yield) and **104** (38% yield) are not known. It is very much possible that both the isomers were formed, but only one crystallized and could thus be isolated[8b].

On the basis of these results, one can interpret the influence of trifluoroacetic acid and its anhydride on the reactions of **2a** with norbornene, cyclopentene, and *trans*-cyclooctene mentioned in *Sections 3.2* and *3.3*. The presence of the catalyst not only accelerated the cycloaddition reactions but also the γ-keto ketenes could no longer be observed as intermediates, although the same enol lactones (**21a, 31, 36a**) were produced[4].



21

62a 105 63a

Most likely, the transient 4,5-dihydropyrylium-2-olates of type **62a** formed by nitrogen extrusion from the primary cycloadducts are protonated at the enolate β-carbon as discussed in the case of the hydrogen chloride addition (eq. *21*). The resulting carbenium-oxonium ion **105** would then lose its most acidic proton to give the enol lactons **63a**. The fact that the reaction of **2a** with norbornene in the presence of deuteriotrifluoroacetic acid selectively gives rise to the 6-*endo*-deuteriated **21a** (= **21a**-*d*) may be rationalized in terms of a deuteron transfer to the sterically least hindered side of 4,5-dihydropyrylium-2-olate **92a**, *i.e.* under kinetic control.

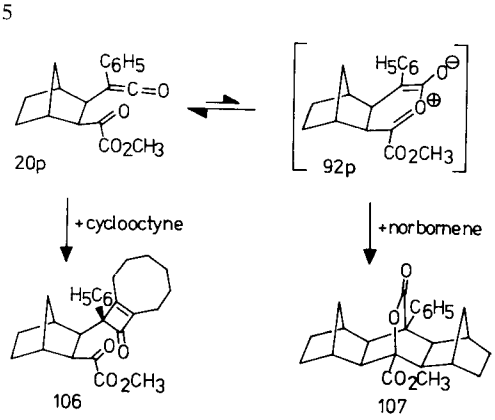
4.3 [2+2]- AND [4+2]-CYCLOADDITIONS

The ability of the ketene functionality in γ-keto ketenes to undergo [2+2]-cycloadditions has already been demonstrated in several of the previous sections. Thus, the γ-keto ketenes **33** and **37** prepared from cyclopentadiene and 2,3-dihydrofuran react smoothly with another molecule of the starting olefins and give rise to the cyclobutanones **34** and **38**, respectively (see *Section 3.3*). Intramolecular cyclobutanone formation is encountered in the reactions **49** → **50** and **51** → **52** (see *Section 3.4*). The intramolecular [2+2]-cycloadditions of the ketene moiety to a CC σ-bond of a cyclopropane unit lead to the cyclopentanone derivatives **16** (see *Section 3.1*)

Mechanistic considerations discussed above have suggested the existence of 4,5-dihydropyrylium-2-olates (**60**) as precursors for the γ-keto ketenes on one hand and on the other as intermediates in several of their reactions. Thus, the γ-keto ketenes should persist in an equilibrium with the 4,5-dihydropyrylium-2-olates. In order to collect more direct evidence in favour of the intermediacy of **60** we set out to trap it with a proper dienophile, which was supposed to undergo a [4+2]-cycloaddition with the oxadiene system.

Since cyclooctyne had been proved to be very reactive towards oxadiazinones[9], we treated **20p** with this strained alkyne (scheme 15). The only product so far isolated was identified as the cyclobutenone derivative **106** (36% yield) by an X-ray structure analysis[7]. In view of the fact that other ketene adducts of cyclooctyne are not known, the preference for the [2+2]-cycloaddition over the [4+2] mode was not expected.

SCHEME 15



But the desired reaction took place when **20p** and an excess of norbornene were heated at 60 °C for 12 days affording the *saturated* δ-lactone **107** in 50% yield (scheme 15). To the best of our knowledge this provides the first example for the formation of a *saturated* δ-lactone in a [4+2]-cycloaddition. Indeed, norbornene does not show a high activity in Diels-Alder-reactions with inverse electron demand[1b], but as a ketenophile it is much less qualified[28]. Hence, norbornene seems to be properly tuned to intercept **92p** selectively from the equilibrium **20p** ⇌ **92p**.

5. CONCLUDING REMARKS

The described cycloadditions of oxadiazinones with alkynes and alkenes do not only furnish a wide variety of interesting compounds, which are not easily prepared by other synthetic strategies, but also uncovered reaction principles with important mechanistic implications. And still, the exploratory phase of these investigations has not been completed, since only two oxadiazinones, *i.e.* **2a** and **2p** have been examined to date with different kinds of olefins. The differences in reactivity and in the nature of the isolated products give rise to the expectation that further interesting results will be obtained, if the preparation of oxadiazinones with new substitution patterns can be achieved; for instance, methyl 2-phenyl-1,3,4-oxadiazin-6-one-5-carboxylate, the isomer of **2p**, methyl 1,3,4-oxadiazin-6-onecarboxylates with alkyl substituents, and dimethyl 1,3,4-oxadiazine-6-onebisdicarboxylate. The latter diazadiene should be much more reactive than **2p**, and thus, it is hoped that unactivated 1,2-dialkyl- and trialkyl-ethylenes can be added.

The presence of three functional groups in the δ-chloro-δ-lactones **98 - 100** as well as in the oxobisester **95** and in the acids **103, 104** promise some synthetic potential. This could also be valid for enol lactones of type **63**. An illustration is the possible reaction of all these compounds with bifunctional nucleophiles, which could lead to seven-membered or even larger rings. And one should keep in mind that in the formation of oxobisester **95** three stereogenic centres are controlled with high selectivity. Introduction of a properly selected chiral auxiliary group as replacement for the methyl group in **2p** could generate the derived products with an enantiomeric excess. Since asymmetric Diels-Alder additions with inverse electron demand using chiral dienes have not yet been investigated, such a project could result in methodologies complementary to those provided by the normal Diels-Alder addition[29]. These prospects may suffice to predict convincingly that the chemistry of oxadiazinones will furnish many more rewarding results.

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