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Reactivity of Pyrrole Pigments. Part VII[1] Autoxidation of Model Compounds for 5(2*H*)-Dipyrrylmethanones and 3,4-Dihydro-5(1*H*)-Pyrromethenones

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The autoxidation in alkaline media and in the dark of some 5-methyl substituted 3,4-dimethyl-3-pyrrolin-2-ones and 5-methylene substituted pyrrolidin-2-ones is studied. Both types of compounds are found to give autoxidation products that indicate very characteristic reaction pathways.

(Keywords: Autoxidation; Bile pigments; Dihydropyrromethenones; Dipyrrylmethanones)

Reaktivität der Pyrrolpigmente, 7. Mitt.: Autoxidation von Modellverbindungen für 5(2H)-Dipyrrylmethanone und 3,4-Dihydro-5(1H)-pyrromethenone

Es wird die Autoxidation von einigen 5-methylsubstituierten 3,4-Dimethyl-3-pyrrolin-2-onen und 5-methylensubstituierten Pyrrolidin-2-onen in alkalischem Medium untersucht. Für beide Verbindungstypen wurden charakteristische Reaktionswege gefunden.

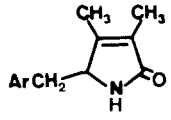
Introduction

The term autoxidation reaction applies to the atmospheric oxidation without combustion of C—H bonds. Generally, autoxidation reactions proceed faster in alkaline media. Some autoxidations can be catalyzed by light: one reaction of this type is very characteristic for bilirubin IX α[2a]. Despite the published work about autoxidation and singlet oxygen oxidation of bilirubin IX α and related compounds[2], to our knowledge no paper has appeared on the reactions of oxygen with bile pigments possessing not fully unsaturated end rings. In order to predict the

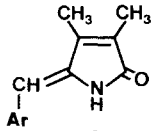
reactivity of 5(2*H*)-dipyrrylmethanones and 3,4-dihydro-5(1*H*)-pyrromethenones towards oxygen, we have studied the autoxidation in alkaline media and in the dark of model compounds with 5-methyl-3-pyrrolin-2-one (**1**) and 5-methylene-pyrrolidin-2-one (**6**) partial structures.

We chose the compounds **1a**, **1b**, **1c**, and **1d**, and **6a**, **6b**, and **6c** as model compounds due to their synthetic accessibility, and in the case of compounds of type **6**, also to decrease the complexity of the reaction mixture, avoiding the possibility of *cis-trans* isomerism. The experimental method selected was the simple chemical separation and analysis of the reaction products from each substrate autoxidation, following exposure of alkaline methanol solutions at room temperature and in the dark to air.

The results here described—due to the nature of the model compounds studied—can only give an indication of the autoxidation behaviour of the lactam rings of 4,5-dihydro or 2,3-dihydro bile pigments, but not of the reactivity of the other parts of these molecules. Consequently, our results can only be extrapolated to tetrapyrroles with the warning that not necessarily the first atom to be oxidized will be one in these end rings.



1



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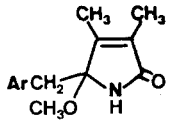

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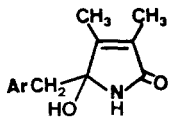

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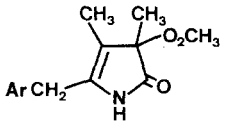


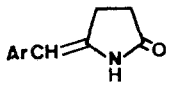
5

	Ar
a	p-$CH_3C_6H_4$-
b	o-$CH_3C_6H_4$-
c	2-pyrrolyl
d	1-CH_3-2-pyrrolyl

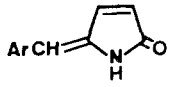
Results and Discussion

The Tables 1 and 2 show the results for the autoxidation of model compounds with one double bond either between the carbon atoms 3 and 4 (**1**) or with an exocyclic double bond (**6**) respectively. A clear oxidation pattern was observed for the first series (**1**; see Table 1) that made it

possible to identify all reaction products. For the second series (**6**; see Table 2) only identification of the principal reaction products was possible; however, the same Table shows that besides the reaction products—similar to those obtained for the first series (i.e. **7** and **8**)—other compounds appear, corresponding to a fragmentation reaction (**9**, **10**, and **11**).



6



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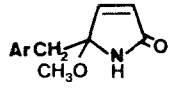

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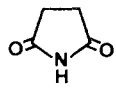
9

10



11

	Ar
a	C_6H_5–
b	2-pyrrolyl
c	1-CH_3-2-pyrrolyl

Not all compounds of the Tables 1 and 2 were accessible in a pure form, nor even in enough quantity to permit the report of a full set of physical data. This difficulty arose especially for the autoxidation products of **6**. However, all compounds reported were identified by their spectral properties as described in the experimental part.

It is generally accepted[3] that the autoxidation in alkaline media initiates and propagates through a substrate radical, as indicated below:

$$RH + Base^- \rightarrow HBase + R^-$$
$$R^- + O_2^- \rightarrow R\cdot + O_2^- \qquad \textit{Initiation (I)}$$

$$R\cdot + O_2 \rightarrow ROO\cdot$$
$$ROO\cdot + R^- \rightarrow ROO^- + R\cdot \qquad \textit{Propagation (II)}$$

Table 1. *Reaction products from the autoxidation in alkaline methanol in the dark*[a] *of some 5-methyl substituted 3-pyrrolin-2-ones* (**1**)

Substrate	Percentages on the final reaction mixture (%)				
	1	**2**	**3**	**4**	**5**
1a	15	5	60	15	5
1b	5	9	63	18	5
1c	24	traces	66	traces	8
1d	10	8	64	10	8

[a] For experimental conditions see Experimental part.

The reaction pathways proposed to explain the results reported, are based on this mechanism and on the assumption that under our experimental conditions (in the dark) singlet oxygen is not present. It has been reported[4a] that several chemical reactions generate singlet oxygen (e.g. by ozonation of some aldehydes[4b]); nevertheless, we think that in our experiments this is very unlikely. Even so, we are not providing any experimental evidence of its absence, due to the intrinsic and well known difficulty to completely exclude singlet oxygen in such oxidation processes.

Table 2. *Reaction products from the autoxidation in alkaline methanol in the dark*[a] *of some 5-methylene substituted pyrrolidin-2-ones* (**6**)

Substrate	Percentages on the final reaction mixture (%)				
	6	**7**	**8**	**9 + 10**	**11**
6a	traces	10 ± 5	20 ± 5	25 ± 5	25 ± 5
6b	20 ± 5	10 ± 5	50 ± 5	$\simeq 5$	$\simeq 5$
6c	traces	10 ± 5	$\simeq 5$	30 ± 5	30 ± 5

[a] For experimental conditions see Experimental part.

3,4-Dimethyl-5-arylmethyl-3-pyrrolin-2-ones (**1**)

1a–1d were synthesized by reduction with sodium dithionite from the corresponding unsaturated compounds **2**. Sodium dithionite is described in the literature[5a] as a reducing agent for olefinic double bonds conjugated to electron-withdrawing groups. The results obtained in our laboratory[5b] using this agent on bile pigments will be reported elsewhere, but a general reduction procedure is described in the experimental part.

To explain the reaction products from the autoxidation of the type **1** compounds (see Table 1), we propose the mechanism of Fig. 1. In such systems (**1**), the more stable carbanion is the one produced by deprotonation at the carbon-5 atom[6] (**a** in Fig. 1). Oxidation of this carbanion gives an allylic radical (**b**) with higher electron density at the carbon atoms 3 and 5, which makes them the most reactive ones. Thus, radical **b** explains the formation of the peroxide **5** by attack to the carbon atom 3; however, an analogous peroxide or hydroperoxide on the carbon atom 5 has not been detected. On the other side, analogous derivatives to the 5-methoxy or 5-hydroxy compounds **3** and **4** (but attached to carbon-3) were not present in the reaction mixture. We explain the appearingly different reactivity between atoms 3 and 5 in terms of the elimination of a

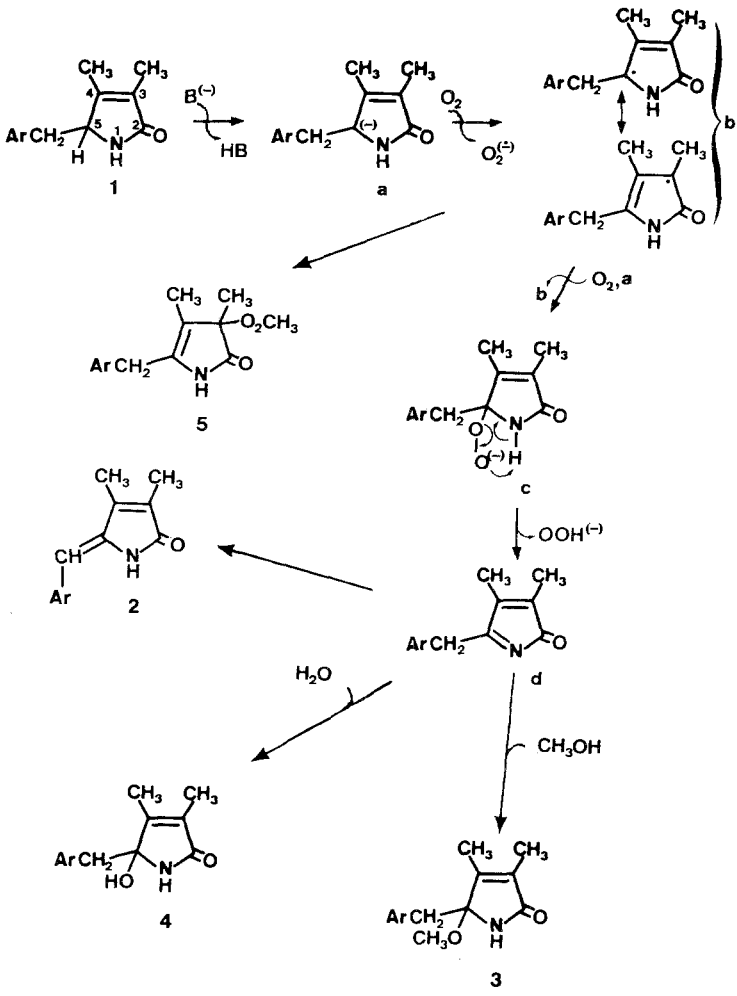


Fig. 1. Reaction pathways proposed for the base catalyzed autoxidation in the dark of the type **1** compounds

hydroperoxide anion from the peroxide anion **c**, formed as the final product of the propagation step (II) in the autoxidation process; this elimination would be favoured by the formation of an aromatic (6π) electrons activated complex. Such an elimination should also be possible through the neutral peroxide radical obtained in the first stage of the propagation step (II). The 2-oxo-2*H*-pyrrole **d**, formed by this elimination is a structure (detected in the propentdyopents of the pro-type

dipyrromethene[7]) adding water and related nucleophiles easily; the addition of water or methanol should give **4** and **3**, respectively, and its tautomerization should give **2**. The compounds of type **2** can also appear by water or methanol elimination from **4** or **3**, but under our experimental conditions—alkaline methanol—it is more plausible to be derived from **d**.

5-Arylmethylene-pyrrolidin-2-ones (**6**)

6a—**6c** were synthesized following the method of *Gossauer*[8] for 3,4-dihydro-5(1*H*)-pyrromethenones: the δ-diazolevulinic acid methyl ester was coupled with phenyl copper (for **6a**) or with the corresponding pyrrole in the presence of copper (for **6b** and **6c**). After this coupling reaction, the lactam ring was built by cyclization with ammonium acetate.

The mixture of the autoxidation reaction products of **6** contains compounds **7** and **8** (analogous to compounds **2** and **3** obtained in the autoxidation of compounds of type **1**), plus the fragmentation products **9**, **10**, and **11**. The presence of compounds **7** and **8** can be explained through base catalyzed tautomerization of **6** to 5-methyl-3-pyrrolin-2-ones (compounds of type **1**) and subsequent autoxidation. This tautomerization follows a well known mechanism described by *Gossauer*[9], which implicates tautomerization through 5-methyl-3,4-dihydro-2-oxo-2*H*-pyrroles and 5-methyl-4-pyrrolin-2-ones. Thus, to account for the reaction products obtained from the base catalyzed autoxidation of **6a**, **6b**, and **6c**, we propose the reaction pathways shown in Fig. 2. In order to simplify that figure, we have not represented the carbanions R^-, which during the initiation and propagation steps (I and II) originate the corresponding radicals $R\cdot$. The compounds of type **6** can also be deprotonated at the carbon atom α to the carbonyl group, but we suppose the free radical from this carbanion rearranges to the radical **t**. Consequently, the formation of **7** and **8** directly from **5** cannot be excluded; nevertheless, we think that **7** and **8** are obtained because of the tautomerization of **6**: the radical **t** must follow an autoxidation pathway similar to the radical **b** (Fig. 1). The fate of the radicals **r** and **s** is determined by the attack of O_2 to the most reactive benzylic carbon atom giving the peroxide anions **u** and **v** respectively. These peroxides would give the *endo*-peroxide **x**, which solvolyses to succinimide (**11**) and aldehyde **9**. The aldehydes **9** were only detected in minute amounts together with the carboxylic acids **10**. We think that **9** is formed first and then it autoxidizes to **10**; we have proved that under the presented experimental conditions **9a** oxidizes quantitatively to the carboxylic acid **10a**. Obviously, in all experiments the sum of **9** plus **10** was equimolecular to succinimide (**11**).

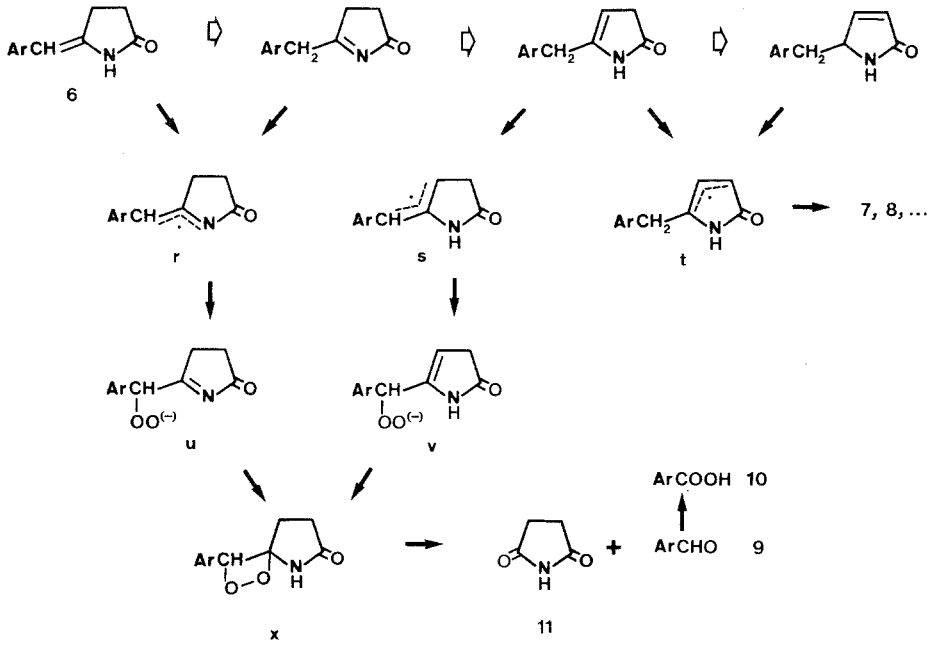


Fig. 2. Reaction pathways proposed for the base catalyzed autoxidation in the dark of the type **6** compounds

The autoxidation of **6a** in acidic media (see Experimental part) gives quantitatively **9a**, **10a**, and **11**. In this case the reaction can also be explained supposing rearrangement of the protonated hydroperoxide[10] through an oxenium cation, followed by solvolysis to **9** and **10**. **6b** and **6c** also give the succinimide and the corresponding aldehydes in high yield, though not quantitatively.

Final Remarks

From the results reported above two conclusions can be reached: a) the autoxidation in the dark of 5-methyl-3-pyrrolin-2-ones does not give fragmentation products, and b) the autoxidation in the dark of 5-methylene-pyrrolidin-2-ones, and probably also that of 5-methyl-3,4-dihydro-2*H*-pyrrole-2-ones does give fragmentation products similar to those expected from singlet oxygen oxidation. These observations must be taken into account in the study of autoxidation processes of bile pigments with partially saturated lactam rings.

Experimental

Melting points were determined on a *Kofler*-Reichert microhot stage apparatus. Preparative thin layer chromatography (PTLC) was carried out on 20 × 20 cm plates using 60 HF_{254} silica (1 mm thickness). All products separated by PTLC were subsequently purified by chromatography on a small column of Merck 60 (230–400 mesh) silica. High pressure liquid chromatography was carried out on RadialPak silica columns with a Waters double pump using a variable wavelenght detector 5 FA 339. Preparative HPLC (PHPLC) at the semimicro scale was carried out through repetitive injection using the same system and conditions as for HPLC. UV/VIS spectra were recorded on a Perkin Elmer Lambda 5 instrument. IR spectra were recorded on a Perkin Elmer 681 spectrometer. Mass spectra (MS) on a Hewlett Packard 5700-A instrument. ^{1}H-NMR spectra were determined on a Varian XL 200 (200 MHz) instrument or on a Perkin Elmer R 12 A (60 MHz) instrument.

The synthesis and properties of the following compounds are described in the literature: **2a**[11], **2b**[12], **2c**[13], **2d**[14], **7b**[15], **7c**[15].

General Procedure for the Preparation of **1a**, **1b**, **1c**, *and* **1d**, *from 5-Arylmethylene-3,4-dimethyl-3-pyrrolin-2-ones* (**2**) *by Reduction with Sodium Dithionite*

0.376 mmol of **2**, 120 mg of sodium dithionite (85%) and 126 mg of sodium hydrogen carbonate were dissolved in 4 ml of *DMF*/H_2O (1/1). The mixture was heated for one hour at 90° while stirring under argon atmosphere. After cooling, 50 ml of H_2O were added. Extraction with $CHCl_3$ and evaporation afforded either pure reduced compound **1** or **1** together with some starting material. In the last case separation by PTLC was followed.

3,4-Dimethyl-5-[(4-methylphenyl)methyl]-3-pyrrolin-2-one (**1a**, $C_{14}H_{17}NO$)

Prepared from **2a**, following the general procedure, in 97% yield; m.p. 136–141°.

^{1}H-NMR (δ, $CDCl_3$, 200 MHz): 7.05 (m, center of the aromatic AA'BB' system), 5.76 (broad s, NH), 4.04 (m, J_{AM} = 4.0 Hz, J_{AX} = 10.6 Hz, H-5), 3.16 (dd, J_{AM} = 4.0 Hz, J_{MX} = 13.2 Hz, $ArCH_X$—H_M), 2.35 (dd, J_{AX} = 10.6 Hz, J_{MX} = 13.2 Hz, $ArCH_M$—H_X), 2.32 (s, $ArCH_3$), 1.96 (m, CH_3-4), 1.79 (m, CH_3-3).

IR (KBr): 3210, 3060, 1680, 770 cm^{-1}.

UV/VIS [λ_{max} nm (ε), iso-octane]: 211 (16900), 219 (15400).

MS (*m*/e, 70 eV): 215 (M^+, 10%), 110 (37), 105 (100), 91 (10).

3,4-Dimethyl-5-[(2-methylphenyl)methyl]-3-pyrrolin-2-one (**1b**, $C_{14}H_{17}NO$)

Prepared from **2b**, following the general procedure, in 98% yield; m.p. 121–126°.

^{1}H-NMR (δ, $CDCl_3$, 200 MHz): 7.18 (m, center of the aromatic AA'BB' system), 5.79 (broad s, NH), 4.04 (m, J_{AX} = 11.4 Hz, J_{AM} = 3.4 Hz, H-5), 3.22 (dd, J_{MX} = 13.6, J_{AM} = 3.4 Hz, $ArCH_X$—H_M), 2.34 (dd, J_{AX} = 11.4 Hz, J_{MX} = 13.6 Hz, $ArCH_M$—H_X), 2.02 (m, CH_3-4), 1.82 (m, CH_3-3).

IR (KBr): 3200, 3060, 1665, 760, 745 cm^{-1}.

MS (*m*/e, 70 eV): 215 (M^+, 18%), 110 (100), 105 (94).

3,4-Dimethyl-5-[(2-pyrrolyl)methyl]-3-pyrrolin-2-one (**1c**, $C_{11}H_{14}N_2O$)

Prepared from **2b**, according to the general procedure, followed by through PTLC [$CHCl_3/CH_3CN$ (5/1)] of the final residue, in 51% yield; m.p. 111–113°.

^{1}H-NMR (δ, $CDCl_3$, 200 MHz): 8.70 (broad s, NH), 6.74 (broad s, NH), 6.68, 6.13, and 5.98 (m, pyrrole CH), 4.08 (m, $J_{AX} = 8.8$ Hz, $J_{AM} = 3.2$ Hz, H-5), 3.16 (dd, $J_{MX} = 14.6$ Hz, $J_{AM} = 3.2$ Hz, $ArCH_X$—H_M), 2.55 (dd, $J_{MX} = 14.6$ Hz, $J_{AX} = 8.8$ Hz, $ArCH_M$—H_X), 1.98 (m, CH_3-4), 1.81 (m, CH_3-3).

IR (KBr): 3300, 3100, 3075, 1690, 715 cm^{-1}.

UV/VIS [λ_{max} nm (ε), CH_3OH]: 220 (7100).

MS (*m/e*, 70 eV): 190 (M^+, 2%), 145 (2), 110 (7), 82 (15), 80 (100).

3,4-Dimethyl-5-[(1-methyl-2-pyrrolyl)methyl]-3-pyrrolin-2-one (**1d**, $C_{15}H_{19}NO$)

Prepared from **2d**, according to the general procedure, followed by PTLC [$CHCl_3/CH_3CN$ (5/1)] of the final residue, in 60% yield; m.p. 138–141°.

^{1}H-NMR (δ, $CDCl_3$, 200 MHz): 6.59, 6.09, and 5.99 (m, pyrrole CH), 6.02 (broad s, NH), 4.08 (m, $J_{AX} = 11.2$ Hz, $J_{AM} = 3.4$ Hz, H-5), 3.56 (s, NCH_3), 3.09 (dd, $J_{AM} = 3.4$ Hz, $J_{MX} = 12.3$ Hz, $ArCH_X$—H_M), 2.37 (dd, $J_{AX} = 11.2$ Hz, $J_{MX} = 12.3$ Hz, $ArCH_M$—H_X), 1.98 (m, CH_3-4), 1.81 (m, CH_3-3).

IR (KBr): 3195, 3050, 1675, 710 cm^{-1}.

UV/VIS [λ_{max} nm (ε), CH_3OH]: 209 (19900).

MS (*m/e*, 70 eV): 204 (M^+, 1%), 110 (1), 94 (100).

5-Phenylmethylene-pyrrolidin-2-one (**6a**, $C_{11}H_{11}NO$)

215 mg (0.978 mmol) of ethyl 5-phenyl-4-oxo-pentanoate are heated 20 min at 130° together with 3.84 g of melting ammonium acetate. After cooling aqueous ammonia (17–20%) is added until alkaline *pH*, and the solution is extracted three times with $CHCl_3$. The organic phase is washed with water, dried with Na_2SO_4, and rotoevaporated. PTLC of the residue [$CHCl_3/CH_3CN$ (30/1); R_f 0.57 (*Z*) and 0.36 (*E*)] affords (*Z*)- and (*E*)-**6a** in 80% total yield. The relative ratio of (*E*) and (*Z*) isomers is 75/25. (*E*)-**6a**: m.p. 103–108°.

^{1}H-NMR (δ, $CDCl_3$, 60 MHz): 7.7 (broad s, NH), 7.18 (m, center of the aromatic AA'BB'C system), 5.85 (broad s, =CH), 3.0 (m, CH_2-4), 2.6 (m, CH_2-3).

IR (KBr): 3150, 3060, 1745, 1665, 690 cm^{-1}.

UV/VIS [λ_{max} nm (ε), C_2H_5OH]: 283 (22700).

MS (*m/e*, 70 eV): 173 (M^+, 100%), 145 (30), 144 (97), 130 (27), 77 (8).

(*Z*)-**6a**: m.p. 113–116°.

^{1}H-NMR [δ, $CDCl_3$, 200 MHz]: 7.70 (broad s, NH), 7.25 (m, center of the aromatic AA'BB'C system), 5.52 (broad s, =CH), 2.93 (m, CH_2-4), 2.55 (m, CH_2-3).

IR (KBr): 3220, 1720, 1665, 690 cm^{-1}.

UV/VIS [λ_{max} nm (ε), CH_3OH]: 269 (13300).

MS (*m/e*, 70 eV): the same as for (*E*)-**6a**.

Ethyl 4-oxo-5-phenyl-pentanoate ($C_{13}H_{16}O_3$)

Phenyl copper was obtained from phenyl lithium following the procedure described in the literature[16]. To the suspension of phenyl copper (obtained from 23.1 mmol of phenyl lithium in 140 ml of ethyl ether), 1.15 g of ethyl 5-diazo-5-oxo-pentanoate[17] (75% pure, determined by ^{1}H-NMR) was added slowly at —25° while stirring under argon atmosphere. After 1 hour stirring at room temperature, 25 ml 2 *N* HCl were added slowly. Filtration and separation of the organic phase

(washed with water and the water phase extracted with ether) afforded after drying with Na_2SO_4 and evaporation 1.685 g of a red oil. Column chromatography with *n*-hexane, *n*-hexane/benzene, benzene, and toluene yielded in the central fractions a mixture of diethyl succinate and ethyl 4-oxo-5-phenyl-pentanoate. The last was obtained pure by vacuum distillation (0.001 mm Hg) at 80–90° (40–50° for diethyl succinate). 62% yield (referred to the initial diazoketone).

^{1}H-NMR (δ, $CDCl_3$, 60 MHz): 7.21 (m, center of the aromatic AA'BB'C system), 4.05 (q, $J = 7$ Hz, OCH_2), 3.62 (s, $ArCH_2$), 2.52 (m, center of a AA'BB' system, CH_2—CH_2), 1.20 (t, $J = 7$ Hz, CH_3).

IR (KBr): 1735, 1720, 1200, 700 cm^{-1}.

MS (*m*/e, 70 eV): 220 (M^+, 4%), 175 (14), 174 (4), 143 (11), 142 (4), 129 (37), 115 (13), 114 (10), 101 (100), 91 (59), 73 (24).

5-[(2-Pyrrolyl)methylene]-pyrrolidin-2-one (**6b**; $C_9H_{10}N_2O$)

Obtained from 50 mg (0.24 mmol) of ethyl 4-oxo-5-(2-pyrrolyl)-pentanoate and 1.158 (13 mmol) ammonium acetate following the procedure described above for **6a**. The crude reaction product was purified by column chromatography on silica gel, giving 30% yield of a mixture of the **6b** stereoisomers (*E*) and (*Z*) (7 : 3). PTLC permited to isolate pure (*E*) isomer.

(*E*)-**6b**: m.p. 179–183° d.

^{1}H-NMR (δ, $CDCl_3$, 200 MHz): 6.63, 6.08, and 5.92 (m, pyrrole CH), 5.82 (t, $J = 2.0$ Hz, =CH), 2.94 (m, CH_2-4), 2.56 (m, CH_2-5).

IR (KBr): 3410, 1730, 1660, 730 cm^{-1}.

UV/VIS [λ_{max} nm (ε), CH_3OH]: 289 (11000).

MS (*m*/e, 70 eV): 162 (M^+, 100%), 113 (68), 119 (8).

Ethyl 4-oxo-5-(2-pyrrolyl)pentanoate ($C_{11}H_{15}NO_3$)

The synthetic method used is analogous to the one described in the literature for ethyl 4-oxo-5-(1-methyl-2-pyrrolyl)pentanoate[18]. 1.56 (8.823 mmol) of ethyl 5-diazo-5-oxo-pentanoate[15] in 6 ml of dry benzene were added (at 85° with stirring under argon atmosphere) to a suspension of copper powder (0.1 g) in 1.075 g (16 mmol) of pyrrole. 15 min after the gas formation had stopped, the mixture was rotoevaporated and the residue distilled (0.001 mm Hg) to give diethyl succinate (until 50°) and ethyl 4-oxo-5-(2-pyrrolyl)pentanoate (at 110–120°) of 85% purity by ^{1}H-NMR and 61% yield referred to the initial δ-diazoketone.

^{1}H-NMR (δ, $CDCl_3$, 60 MHz): 8.55 (broad s, NH), 6.73, 6.1 (m, pyrrole hydrogens), 4.13 (q, $J = 7$ Hz, O—CH_2), 3.76 (s, *Ar*-CH_2), 2.65 (m, center of AA'BB' system, CH_2—CH_2), 1.24 (t, $J = 7$ Hz, CH_3).

IR (KBr): 3480, 1725, 1190, 725 cm^{-1}.

MS (*m*/e, 70 eV): 209 (M^+, 21%), 164 (21), 163 (27), 136 (8), 129 (16), 101 (46), 80 (100).

5-[1-Methyl-2-pyrrolyl)methylene]-pyrrolidin-2-one (**6c**; $C_{10}H_{12}N_2O$)

Obtained from 60 mg (0.27 mmol) of ethyl 4-oxo-5-(1-methyl-2-pyrrolyl)pentanoate[18] and 1.158 g of ammonium acetate following the procedure described for **6a**. The crude product was purified by PTLC ($CHCl_3/CH_3CN$, 5 : 1) giving **6c** in 67% yield as a mixture of diastereoisomers (*E*) and (*Z*), (6 : 1). The (*E*) and (*Z*) isomers could be separated by PTLC.

(*E*)-**6c**: m.p. 161–164°.

^{1}H-NMR (δ, $CDCl_3$, 200 MHz): 8.04 (broad s, NH), 6.58, 6.16, and 6.01 (m, pyrrole CH), 5.74 (t, J = 2.3 Hz, =CH), 3.56 (s, NCH_3), 2.97 (m, CH_2-4), 2.60 (m, CH_3-3).

IR (KBr): 3170, 3100, 1705, 1665, 710 cm^{-1}.

UV/VIS [λ_{max} nm (ε), CH_3OH]: 292 (15300).

MS (m/e, 70 eV): 176 (M^+, 100%), 175 (7), 147 (97), 133 (23), 132 (30).

(*Z*)-**6c**: m.p. 134–140°.

^{1}H-NMR (δ, $CDCl_3$, 200 MHz): 7.81 (broad s, NH), 6.58, 6.15, and 6.03 (m, pyrrole CH), 5.29 (t, J = 2.3, =CH), 3.54 (s, NCH_3), 2.91 (m, CH_2-4), 2.55 (m, CH_2-3).

IR (KBr): 3270, 3100, 1705, 1670, 715 cm^{-1}.

UV/VIS [λ_{max} nm (ε), CH_3OH]: 288 (2600).

MS (m/e, 70 eV): the same as for (*E*)-**6c**.

General Procedure for the Autoxidation of Type **1** *Compounds in Alkaline Methanol*

35 mg of substrate (compounds **1a–1c**) in 10 ml of 1 *N* methanolic KOH were kept during 84 h in contact with the atmosphere at room temperature and in the dark. After addition of 10 ml water and neutralization with HCl (5%) the solution was extracted several times with $CHCl_3$. The organic phase was washed twice with water, dried with Na_2SO_4 and rotoevaporated. The reaction products were isolated and detected according to the following general procedure. The crude reaction products analyzed by TLC ($CHCl_3/CH_3CN$ mixtures) immediately and after each step of the isolation procedure: no variation was observed in the composition of the reaction mixtures. The obtained yields are shown in the Tables 1 and 2, and were calculated from the ^{1}H-NMR spectra (200 MHz) of each crude reaction mixture.

PHPLC of the crude mixture using $CHCl_3/CH_3CN$/*n*-hexane (79/6/15) as mobile phase at 2 ml/minute, affords three principal fractions between 1.5 and 10 min. The first fraction contains the corresponding 5-methylene-3-pyrrolin-2-ones (**2**) and the peroxides **5**. The second fraction contains the methoxy derivatives **3**, and the initial compounds **1**; and the third fraction contains the hydroxy derivative **4** as principal component. The compounds of type **2** were identified from their mixtures with **5** by TLC, MS, and ^{1}H-NMR by comparison with samples of pure compound. Starting material (**1**) was also identified directly in the mixtures and by TLC comparison with a pure sample. All fractions containing **5** give positive the test for peroxides[19] (KI/starch reagent). Compounds of type **5** were identified by the ^{1}H-NMR, MS, and IR spectra of their mixtures with **2**. **3a** and **3b** were isolated pure; **3c** and **3d** were not isolated pure enough to allow crystallisation; pure **4a** was isolated, but **4b** and **4d** were only identified by the ^{1}H-NMR, IR, and MS spectra of mixtures where these compounds were the principal components; **4c** was only identified by TLC and MS.

The recorded data for the compounds not described in the literature are the following:

3,4-Dimethyl-5-methoxy-5-[(4-methylphenyl)methyl]-3-pyrrolin-2-one (**3a**, $C_{15}H_{19}NO_2$)

Isolated from the autoxidation products of **1a** in alkaline methanol, as indicated in the general procedure; m.p. 97–101°.

^{1}H-NMR (δ, $CDCl_3$, 200 MHz): 7.09 (center of the aromatic AA'BB' system), 5.68 (broad s, NH), 3.14 (d, J = 13.6 Hz, $ArCH_M$—H_A), 2.98 (s OCH_3), 2.71 (d,

$J = 13.6$ Hz, $ArCH_A$—H_M), 2.31 (s, $ArCH_3$), 1.93 (q, $J = 1.2$ Hz, CH_3-4), 1.50 (q, $J = 1.2$ Hz, CH_3-3).

IR (KBr): 3210, 1705, 1675, 1100, 1065, 770 cm^{-1}.

UV/VIS [λ_{max} nm (ε), CH_3OH]: 207 (17500).

MS (*m*/e, 70 eV): 245 (M^+, 2%), 214 (3), 140 (100), 108 (51), 105 (22).

3,4-Dimethyl-5-hydroxy-5-[(4-methylphenyl)methyl]-3-pyrrolin-2-one (**4a**, $C_{14}H_{17}NO_2$)

Isolated from the autoxidation products of **1a** in alkaline methanol, as indicated in the general procedure; m.p.: decomposition above 131°.

^{1}H-NMR (δ, $CDCl_3$, 200 MHz): 7.13 (center of the aromatic AA'BB' system), 5.87 (broad s, NH), 3.16 (d, $J = 13.8$ Hz, $ArCH_M$—H_A), 2.70 (d, $J = 13.8$ Hz, $ArCH_A$—H_M), 2.33 (s, $ArCH_3$), 1.99 (q, $J = 1.2$ Hz, CH_3-4), 1.73 (q, $J = 1.7$ Hz, CH_3-3), 1.58 (broad s, OH).

IR (KBr): 3300, 1705, 1675, 1070, 770 cm^{-1}.

UV/VIS [λ_{max} nm (ε), CH_3OH]: 212 (13500).

MS (*m*/e, 70 eV): 231 (M^+, 2%), 213 (5), 126 (65), 108 (44), 106 (100), 105 (32), 91 (50).

3,4-Dimethyl-4-methylperoxy-2-[(4-methylphenyl)methyl]-2-pyrrolin-5-one (**5a**, $C_{15}H_{19}NO_3$)

Isolated together with **2a** from the autoxidation products of **1a** in alkaline methanol, as indicated in the general procedure. The data from the spectra of the mixture are:

^{1}H-NMR (δ, $CDCl_3$): 7.13 (center of the aromatic AA'BB' system), 5.13 (broad s, NH), 3.12 (d, $J = 13.6$ Hz, $ArCH_M$—H_A), 3.08 (s, $OOCH_3$), 2.95 (d, $J = 13.6$ Hz, $ArCH_M$—H_{AV}), 2.37 (s, $ArCH_3$), 1.50 (s, CH_3-4), 1.44 (s, CH_3-3).

IR (KBr): 1715, 1185 cm^{-1}.

MS (*m*/e, 70 eV): 261 (M^+, 1%), 230 (1), 156 (100), 105 (29).

3,4-Dimethyl-5-methoxy-5-[(2-methylphenyl)methyl]-3-pyrrolin-2-one (**3b**, $C_{15}H_{19}NO_2$)

Isolated from the autoxidation products of **1b** in alkaline methanol, as indicated in the general procedure; m.p. 114–117°.

^{1}H-NMR (δ, $CDCl_3$, 200 MHz): 7.26–7.16 (aromatic hydrogens), 5.56 (broad s, NH), 3.26 (d, $J = 14.0$ Hz, $ArCH_M$—H_A), 2.94 (s, OCH_3), 2.70 (d, $J = 14.0$ Hz, $ArCH_A$—H_M), 2.33 (s, $ArCH_3$), 1.91 (q, $J = 1.2$ Hz, CH_3-4), 1.83 (q, $J = 1.2$ Hz, CH_3-3).

IR (KBr): 3240, 1700, 1110, 1060, 760, 745 cm^{-1}.

UV/VIS [λ_{max} nm (ε), CH_3OH]: 207 (17000).

MS (*m*/e, 70 eV): 245 (M^+, 3%), 214 (3), 140 (100), 108 (69), 105 (34).

3,4-Dimethyl-5-hydroxy-5-[(2-methylphenyl)methyl]-3-pyrrolin-2-one (**4b**, $C_{14}H_{17}NO_2$)

Isolated from the autoxidation products of **1b** in alkaline methanol, as indicated in the general procedure as a mixture with **2b**.

^{1}H-NMR (δ, $CDCL_3$, 200 MHz): 7.15–7.09 (aromatic system), 3.19 (d, $J =$

13.8 Hz, $ArCH_A$—H_M), 2.91 (d, J = 13.8 Hz, $ArCH_M$—H_A), 2.33 (s, $ArCH_3$), 1.95 (q, J = 1.2 Hz, CH_3-4), 1.66 (q, J = 1.2 Hz, CH_3-3), 1.6 (broad s, OH).

UV/VIS [λ_{max} nm (ε), CH_3OH]: no absorption above 210 nm.

MS (m/e, 70 eV): 231 (M^+), 126, 108, 105.

3,4-Dimethyl-4-methylperoxy-2-[(2-methylphenyl)methyl]-2-pyrrolin-5-one (**5b**, $C_{15}H_{19}NO_3$)

Isolated together with **2b** from the autoxidation products of **1b** in alkaline methanol, as indicated in the general procedure. The data from the spectra of the mixture are:

^{1}H-NMR (δ, $CDCl_3$, 200 MHz): 7.3–7.1 (aromatic hydrogens), 3.05 (s, $OOCH_3$), 2.33 (s, $ArCH_3$), 1.50 (s, CH_3-4), 1.46 (s, CH_3-3).

MS (m/e, 70 eV): 261 (M^+), 156, 105.

3,4-Dimethyl-5-methoxy-5-[(2-pyrrolyl)methyl]-3-pyrrolin-2-one (**3c**, $C_{12}H_{16}N_2O_2$)

Isolated as an oil from the autoxidation products of **1c** in alkaline methanol, as indicated in the general procedure.

^{1}H-NMR (δ, $CDCl_3$, 200 MHz): 8.65 (broad s, pyrrole NH), 6.73, 6.10, and 5.97 (m, pyrrole CH), 5.76 (broad s, lactam NH), 3.18 (d, J = 14.8 Hz, $ArCH_M$—H_A), 3.05 (s, OCH_3), 2.76 (d, J = 14.8 Hz, $ArCH_A$—H_M), 1.83 (q, J = 1.2 Hz, CH_3-4), 1.80 (q, J = 1.2 Hz, CH_3-3).

IR (KBr): 3315, 1695, 1120, 1060, 715 cm^{-1}.

UV/VIS [λ_{max} nm (ε), CH_3OH]: 208 (17000).

MS (m/e, 70 eV): 220 (M^+, 4%), 189 (5), 140 (88), 108 (71), 80 (100).

3,4-Dimethyl-4-methylperoxy-2-[(2-pyrrolyl)methyl]-2-pyrrolin-5-one (**5c**, $C_{12}H_{16}N_2O_3$)

Isolated as an oil from the autoxidation products of **1c** in alkaline methanol, as indicated in the general procedure.

^{1}H-NMR (δ, $CDCl_3$, 200 MHz): 8.43 (broad s, pyrrole NH), 6.73, 6.11, and 6.03 (m, pyrrole CH), 5.25 (broad s, lactam NH), 3.16 (s, $OOCH_3$), 3.14 (d, J = 15.0 Hz, $ArCH_M$—H_A), 3.02 (d, J = 15.0 Hz, $ArCH_A$—H_M), 1.50 (s, CH_3-4), 1.41 (s, CH_3-3).

IR (KBr): 3325, 1720, 1185, 1055, 720 cm^{-1}.

UV/VIS [λ_{max} nm (ε), CH_3OH]: 210 (20000).

3,4-Dimethyl-5-methoxy-5-[(1-methyl-2-pyrrolyl)methyl]-3-pyrrolin-2-one (**3d**, $C_{13}H_{18}N_2O$)

Isolated from the autoxidation products of **1d** in alkaline methanol as indicated in the general procedure. The isolated product is more than 90% pure.

^{1}H-NMR (δ, $CDCl_3$, 200 MHz): 6.58, 6.06, and 6.02 (m, pyrrole CH), 5.79 (broad s, NH), 3.60 (s, NCH_3), 3.16 (d, J = 16.0 Hz, $ArCH_M$—H_A), 2.96 (s, OCH_3), 2.56 (d, J = 16.0 Hz, $ArCH_A$—H_M), 1.88 (q, J = 1.2 Hz, CH_3-4), 1.83 (q, J = 1.2 Hz, CH_3-3).

IR (KBr): 3265, 1700, 1220, 1060, 710 cm^{-1}.

UV/VIS [λ_{max} nm (ε), CH_3OH]: 210 ($\simeq$ 14000).

3,4-Dimethyl-5-hydroxy-5-[(1-methyl-2-pyrrolyl)methyl]-3-pyrrolin-2-one (**4d**, $C_{11}H_{14}N_2O_2$)

Isolated from the autoxidation products of **1d** in alkaline methanol, as indicated in the general procedure. The isolated product is more than 90% pure.

^{1}H-NMR (δ, $CDCl_3$, 200 MHz): 6.62, 6.08, and 6.06 (m, pyrrole CH), 5.90 (broad s, NH), 3.63 (s, NCH_3), 3.18 (d, $J = 14.8$ Hz, $ArCH_A$—H_M), 2.66 (d, $J = 14.8$ Hz, $ArCH_M$—H_A), 2.44 (broad s, OH), 1.99 (q, $J = 1.0$ Hz, CH_3-4), 1.78 (q, $J = 1.0$ Hz, CH_3).

IR (KBr): 3330, 1695, 1185, 1060, 710 cm^{-1}.

UV/VIS [λ_{max} nm (ε), CH_3OH]: 207 ($\simeq$ 15000).

MS (*m*/e, 70 eV): 220 (M^+, 1%), 202 (4), 126 (4), 108 (6), 94 (100).

3,4-Dimethyl-4-methylperoxy-2-[(1-methyl-2-pyrrolyl)methyl]-2-pyrrolin-5-one (**5d**, $C_{13}H_{18}N_2O_3$)

Isolated together with **2d** from the autoxidation products of **1d** in alkaline methanol, as indicated in the general procedure. The data from the spectrum of the mixture are:

^{1}H-NMR (δ, $CDCl_3$, 200 MHz): 3.58 (s, NCH_3), 3.08 (s, $OOCH_3$), 1.51 (s, CH_3-4), 1.46 (s, CH_3-3).

MS (*m*/e, 70 eV): 250 (M^+), 156.

General Procedure for the Autoxidation of Type **6** *Compounds in Alkaline Methanol*

The experimental procedure was the same as for the compounds of type **1**; however, due to the high solubility in water of some of the oxidation products of **6**, in this case, after the neutralisation with HCl (5%), the solution was rotoevaporated and the residue was dissolved in benzene/methanol (3/1), filtered and rotoevaporated. The quantitative composition of this reaction mixture was determined by ^{1}H-NMR (200 MHz). Identification of the reaction products was achieved by PTLC, MS, IR, and ^{1}H-NMR spectra of the pure compounds or of enriched fractions of them. Some of the separation procedures are described in the general experimental procedure for compounds of type **1**.

Succinimide (**11**) and the carboxylic acids **10**, were always separated and identified together by ^{1}H-NMR of their mixtures and by TLC by comparison with pure samples. The corresponding aldehydes were only detected in very small amounts. The compounds of type **7** were always present as a mixture of the two stereoisomers (*E*) and (*Z*). **7a** and **7b** were only identified by comparison of their spectrometric properties with those of pure analogous compounds of the series and in the case of **7a** also by comparison with *5-(4-methylphenyl)methylene-3-pyrrolin-2-one* (see below).

The recorded data for the compounds not described in the literature are the following:

(Z)-5-[(4-methylphenyl)methylene]-3-pyrrolin-2-one ($C_{12}H_{11}NO$)

Obtained using the general method described in the literature[20] and by column chromatography of the crude mixture reaction in only 2% yield; m.p. 138–142°.

^{1}H-NMR (δ, $CDCl_3$, 200 MHz): 7.92 (broad s, NH), 7.27 (m, $J = 7.9$ Hz, center of the aromatic AA'BB' system), 7.08 (dd, $J = 5.55$ Hz, $J = 1.65$ Hz, 1 H), 6.19 (dd, $J = 5.55$ Hz, $J = 1.65$ Hz, 1 H), 6.10 (broad s, exocyclic =CH), 2.38 (s, $ArCH_3$).

IR (KBr): 3220, 1695, 1680, 1645, 800 cm^{-1}.
UV/VIS [λ_{max} nm (ε), CH_3OH]: 341 (23000).
MS (*m*/e, 70 eV): 160 (M^+, 100%), 132 (25), 131 (41), 106 (13), 105 (38), 104 (36).

(Z)-5-Phenylmethylene-3-pyrrolin-2-one (**7a**, $C_{11}H_{11}NO$)

Isolated from the autoxidation products of **6a** in alkaline methanol as it is indicated in the general procedure. The data from the spectra of the mixture are:
^{1}H-NMR (δ, $CDCl_3$, 200 MHz): Peaks correspond to those of 5-(4-methylphenyl)methylene-3-pyrrolin-2-one.
UV/VIS [λ_{max} nm, CH_3OH]: 327.
MS (*m*/e, 70 eV): 171 (M^+, 100%), 142, 128.

5-Methoxy-5-phenylmethyl-3-pyrrolin-2-one (**8a**, $C_{12}H_{15}NO_2$)

Isolated from the autoxidation products of **6a** in alkaline methanol, as indicated in the general procedure. The data from the spectra of the mixture are:
^{1}H-NMR (δ, $CDCl_3$, 210 MHz): 7.30 (m, aromatic CH), 6.79 (d, J = 5.8 Hz, J = 1.8 Hz, H-4), 6.26 (broad s, NH), 6.07 (dd, J = 5.8 Hz, J = 1.5 Hz, H-3), 3.14 (d, J = 13.8 Hz, $ArCH_M$—H_A), 3.13 (s, OCH_3), 3.05 (d, J = 13.8 Hz, $ArCH_A$—H_M).
MS (*m*/e, 70 eV): 203 (M^+, 1%), 172 (2), 112 (100), 91 (62), 80 (93).

5-Methoxy-5-[(1-methyl-2-pyrrolyl)methyl]-3-pyrrolin-2-one (**8c**, $C_{11}H_{14}N_2O_2$)

Isolated from the autoxidation products of **6c** in alkaline methanol as indicated in the general procedure. The isolated **8c** is more than 90% pure.
^{1}H-NMR (δ, $CDCl_3$, 200 MHz): 6.87 (dd, J = 6.0 Hz, J = 1.8 Hz, H-4), 6.59, 6.08, and 6.02 (m, pyrrole CH), 6.15 (dd, J = 6.0 Hz, J = 1.5 Hz, H-3), 5.82 (broad s, NH), 3.60 (s, NCH_3), 3.15 (d, J = 14.8 Hz, $ArCH_M$—H_A), 3.11 (s, OCH_3), 2.94 (d, J = 14.8 Hz, $ArCH_A$—H_M).
IR (KBr): 3250, 1705, 1080, 720 cm^{-1}.
MS (*m*/e, 70 eV): 206 (M^+, 2%), 175 (1), 112 (2), 94 (100), 80 (13).

Autoxidation of Compounds of Type **6** *in Acidic Media*

To 10 mg of the substrate (**6a–6c**) 100 mg acetic acid were added and the solution kept in the dark in contact with the atmosphere. After 48 h, decomposition of **6a** into the succinimide (**11**) plus a mixture of benzaldehyde (**9a**) and benzoic acid (**10a**) was complete. For the compounds **6b** and **6c**, after one week the decomposition to **11**, and **9** and **10** was important but not quantitative. Identification was made by ^{1}H-NMR, TLC, and MS of the crude reaction mixtures and of enriched fractions of them. This analysis revealed that only starting material, besides **9**, **10**, and **11** were the principal components of the mixture.

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