Direct Oxidation of Alkanoic Acids and their Amides to γ-Lactones by Peroxydisulphate-containing Systems

Gennady I. Nikishin,* Igor V. Svitanko, and Emmanuil I. Troyansky
N. D Zelinsky Institute of Organic Chemistry, U.S.S.R. Academy of Sciences, Moscow, U.S.S.R.

The reaction of one-electron oxidation of alkanoic acids (I) and their amides (VI) on treatment with $Na_2S_2O_8$-containing systems has been studied. As a result of the direct one-pot reaction acids (I) and amides (VI) are converted into γ- and δ-lactones, the reaction being regioselective and leading mainly to γ-lactones in up to 35% yield. The regioselectivity of the oxidative lactonisation depends greatly on the nature of alkyl substituents. The results obtained are presented in terms of a mechanism suggesting the generation of acyloxyl and amidyl radicals from (I) and (VI), respectively, followed by a rearrangement *via* a 1,5- or 1,6-H shift into the corresponding 3- and 4-carboxy- or -carboxamido-alkyl radicals. The latter undergo oxidative cyclisation to produce γ- and δ-lactones. The system $Na_2S_2O_8$–NaCl–NaOH converts carboxamides (VI) into amines with loss of one carbon atom as a result of a Hoffmann type rearrangement.

Reactions of one-electron oxidation of organic compounds including the formation of free radicals have recently become an effective method of organic synthesis.[1] Important among them are the reactions leading to remote functionalization of carboxylic acids and their derivatives, revealing new approaches to polyfunctional compounds, particularly lactones which are parts of many physiologically active substances.[2]

The present paper deals with a direct oxidative lactonization of carboxylic acids and their amides by means of the oxidative system sodium peroxydisulphate–metal chloride.[3,4]

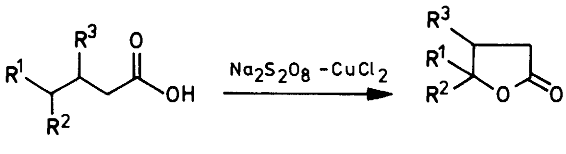
Results and Discussion

The interaction of carboxylic acids with oxidants, *e.g.* derivatives of Pb^{IV}, Ag^{II}, Co^{III} and other polyvalent metals [5–7] or with the oxidative systems $S_2O_8^{2-}$–Ag^+, $S_2O_8^{2-}$–Ag^+–Cu^{2+}, *etc.*[8,9] results usually in their decarboxylation and generation of alkyl free radicals. The maintenance of the carboxylic group in this kind of reactions was only observed when the acids underwent conversion into lactones by peroxydisulphuryl difluoride [10] and on treatment of alkanoic acids bearing a tertiary γ-C atom with the alkaline $KMnO_4$.[11]

We have found that alkanoic acids under the action of 1 : 1 $Na_2S_2O_8$–$CuCl_2$ in aqueous media at 80—90° are converted into γ-lactones (IIa—g) with high selectivity. In the case of acids (Ib—e), along with the predominant formation of γ-lactones (IIb—e), the corresponding δ-lactones (IIIb—e) are formed. Acids (Ia—g) also undergo partial decarboxylation (Table 1).

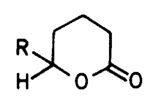
The efficiency of the formation of γ-lactones (II) increases on passing from (Ia) to (Ib) and then decreases from (Ib) to (Ic—e). 3-Methylbutanoic acid (If) is oxidized to β-methyl-γ-butyrolactone (IIf) less effectively than (Ib) to γ-methyl-γ-butyrolactone (IIb). 4-Ethyloctanoic acid (Ig) is selectively oxidized to the γ-lactone (IIg). Therefore the selectivity of the oxidation of (I) to (II) depends greatly on the C-4 substituents of the acids, the contribution of oxidative lactonization being lowest when this atom is primary in (Ia) and (If) and substantially increased when it is secondary in (Ib—e) or tertiary in (Ig).

The contribution of oxidative decarboxylation with CO_2 evolution increases in parallel with a decrease in the lactone yield. During the oxidation of (Ie) 1-chloroheptane was also identified as a result of the interaction of the heptyl radical formed by the decarboxylation of (Ie) with $Na_2S_2O_8$–$CuCl_2$.



(I a-g) (II a-g)

a ; $R^1 = R^2 = R^3 = H$
b ; $R^1 = Me$, $R^2 = R^3 = H$
c ; $R^1 = Et$, $R^2 = R^3 = H$
d ; $R^1 = Pr$, $R^2 = R^3 = H$
e ; $R^1 = Bu, R^2 = R^3 = H$
f ; $R^1 = R^2 = H, R^3 = Me$
g ; $R^1 = Bu, R^2 = Et, R^3 = H$



(III b-e)

b ; R = H
c ; R = Me
d ; R = Et
e ; R = Pr

Table 1. Oxidation of alkanoic acids (Ia—g) in $Na_2S_2O_8$–$CuCl_2$ *

Substrate	Conversion (%)	Reaction products, yield (%) based on the acid converted		
		CO_2	γ-Lactone	δ-Lactone
(Ia)	44	36	(IIa), 34	
(Ib)	45	11	(IIb), 77	(IIIb), 9
(Ic)	45	13	(IIc), 60	(IIIc), 22
(Id)	40	25	(IId), 45	(IIId), 17
(Ie)	31	30 †	(IIe), 30	(IIIe), 12
(If)	30	47	(IIf), 50	
(Ig)	22	27	(IIg), 64	

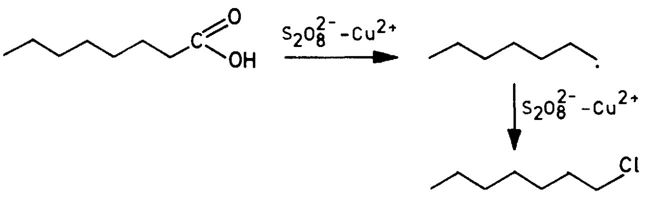
* 85—90°, 5 h; 100 mmol (I), 100 mmol $Na_2S_2O_8$, 100 mmol $CuCl_2 \cdot 2H_2O$; 110 ml water. † 1-Chloroheptane was also identified in 23% yield based on (Ie) converted.

In order to investigate the mechanism of this regioselective oxidative lactonization of acids (I) to γ-lactones (II) and to discover some other effective oxidative systems, a study was made of the oxidation of (I) by means of $Na_2S_2O_8$ in the presence of different salts (Table 2).

Table 2. Oxidation of pentanoic acid (Ib) by $Na_2S_2O_8$–M^nX_n *

			Reaction products, yield (%) based on (Ib) converted		
M^nX_n	Molar ratio $Na_2S_2O_8 : M^nX_n$	(Ib) converted (%)	CO_2	γ-lactone (IIb)	Other products
$CuCl_2$	1 : 1	45	11	77	(IIIb), 9
$CuCl_2$	1 : 2	52	40	38	(IIIb), 4
$CuSO_4$	1 : 1	8	60	Traces	
$CuCl_2$–$FeSO_4$	1 : 1 : 0.1	55	†	55	(IIIb), 4
$FeCl_2$	1 : 1	44	†	40	(IIIb), 4
$FeCl_3$	1 : 1	51	28	47	(IIIb), 8
$CoCl_2$	1 : 1	52	†	30	(IIIb), trace
$Ce_2(SO_4)_3$	1 : 1	44	14	80	
$NiCl_2$	1 : 1	65	8	55	$Cl(CH_2)_4COOH$ (IVa), 14 $C_2H_5CHClCH_2COOH$ (IVb), 15
NaCl	1 : 2	37	8	76	(IIIb), 8

* 85°, 5 h; 100 mmol acid (Ib), 100 mmol $Na_2S_2O_8$, 110 ml water. † Not measured.



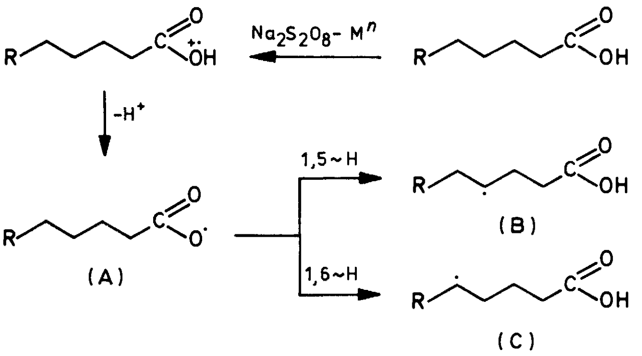
The most effective and selective oxidation of (Ib) to (IIb) occurs with $Na_2S_2O_8$–$CuCl_2$, $Na_2S_2O_8$–$Ce_2(SO_4)_3$, and $Na_2S_2O_8$–$NiCl_2$. The higher the amount of $CuCl_2$, the lower the selectivity of the formation of (II) and the higher the contribution of the decarboxylation reaction. In the presence of Fe^{II}, Fe^{III}, and Co^{II} species the selectivity of the oxidation of (Ib) to (IIb) shows a marked decrease.

$Na_2S_2O_8$–NaCl (1 : 2) converts 25% (Ic), the yield of (IIc) and (IIIc) being 60 and 20%, respectively [based on (Ic) converted].

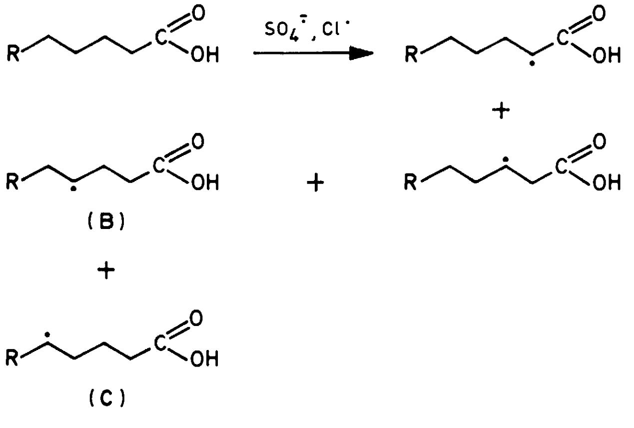
It should be noted that (IIb) is inert to oxidation and undergoes no lactonization when treated with $KMnO_4$–NaOH, used previously to produce lactones from substituted alkanoic acids bearing a tertiary γ-carbon atom[11] (see Experimental section).

We suggest the mechanism of lactone formation involves one-electron oxidation of alkanoic acids by $Na_2S_2O_8$–M^{n+} to acyloxyl radicals of type (A) stabilized by co-ordination with a polyvalent metal. These radicals undergo a 1,5- and 1,6-H shift to rearrange into the 3- and 4-carboxyalkyl radicals (B) and (C). The oxidation of (B) and (C) to the corresponding carbocations and cyclization of the latter or the homolytic cyclization of (B) and (C) by intramolecular addition to the C=O group and subsequent oxidation (*cf.* ref. 12) afford γ- and δ-lactones, respectively (Scheme 1).*

One can also expect the formation of hypochlorites $RCH_2CH_2(CH_2)_2C(O)OCl$ as intermediates with $Na_2S_2O_8$–$CuCl_2$ and $Na_2S_2O_8$–NaCl (*cf.* ref. 13). The homolytic scission of the O–Cl bond results in the generation of radicals which undergo conversion, after being rearranged into (B) and (C), into γ- and δ-lactones.



Scheme 1. M = Cu^{2+}, Ce^{3+}



Scheme 2.

Another possible scheme involves a thermal or a catalytic process in the presence of Cu^{2+} or Ce^{3+}, generating sulphate anion radicals as well as Cl radicals in $Na_2S_2O_8$–$CuCl_2$ and $Na_2S_2O_8$–NaCl. This allows the nonselective abstraction of the hydrogen atoms from the alkyl moiety of the carboxylic acid to generate carboxy-substituted alkyl radicals. Radicals (B) and (C) produce γ- and δ-lactones (Scheme 2).

To refine the proposed mechanism of the oxidation of acids (I) to lactones (II) and (III), a study was made of the interaction of methyl valerate (V) with $Na_2S_2O_8$–$CuCl_2$. Under conditions when no hydrolysis of (V) to produce (Ib)

---

* A referee has suggested that intramolecular hydrogen atom abstraction involves the acyloxy-cation radical rather than the acyloxyl radical, and that proton loss occurs after the hydrogen atom abstraction. Such a scheme is equally compatible with the observed products and is consistent with the formation of lactones, even in the absence of polyvalent metals.

occurs, the conversion of (V) is 8%. Under similar conditions the conversion of (Ib) is 29%, the yield of (IIb) being 24% (see Experimental section). The hydrogen-donating ability of the $CH_3CH_2CH_2CH_2$ moiety in (Ib) and (V) with respect to $SO_4^{-\cdot}$ or Cl· is probably the same and the radical $CH_3\dot{C}HCH_2CH_2C(O)OCH_3$, an analogue of (B), originating from ester (V) can also be oxidized to γ-lactone (IIb) (*cf.* ref. 14) in the oxidative systems containing $Na_2S_2O_8$. We believe that the observed inertness of (V) to $Na_2S_2O_8$–$CuCl_2$ allows us to reject a mechanism of the formation of (IIb) involving initial attack of $SO_4^{-\cdot}$ or Cl· on the alkyl moiety of (Ib). This scheme does not account for the high regioselectivity of the formation of γ-lactones (II) either, compared with that of δ-lactones (III). Due to the fact that the hydrogen atoms are abstracted by the electrophilic radicals usually from the (ω − 1) carbon atom of the alkyl residue[15] the interaction of (Ic) with the electrophilic $SO_4^{-\cdot}$ and Cl· would probably produce predominantly a precursor of δ-lactone (IIIc), the radical $CH_3\dot{C}H(CH_2)_3COOH$, stabilized by interaction with the CH_3 group, the yield of which, however, is considerably lower than that of the corresponding γ-lactone (IIc).

Thus the mechanism involving the generation of *O*-centred acyloxyl radicals as a key step followed by a rearrangement involving a 1,5- or 1,6-H shift to produce 3- and 4-carboxyalkyl radicals seems more reasonable. According to the general principles of rearrangements in radical systems, a 1,5-H shift dominates over a 1,6-one,[16] which is in line with the regioselective formation of γ-lactones (II). According to this scheme the maximum yield of γ-lactones is observed in the oxidation of (Ib) when a 1-methyl-3-carboxypropyl radical stabilized by conjugation with the CH_3 group is generated. The low yield of (IIa) from (Ia) is due to a disadvantage in the rearrangement of the corresponding acyloxyl radical $CH_3CH_2CH_2C(O)O$ to a primary 3-carboxypropyl radical.

In distinction to $Na_2S_2O_8$–$CuCl_2$, $Na_2S_2O_8$–NaCl, and $Na_2S_2O_8$–$Ce_2(SO_4)_3$, there is a contribution, following from the identification of chloro-acids (IVa and b), due to a mechanism involving an initial hydrogen abstraction from the alkyl fragment when (Ib) is oxidized by means of $Na_2S_2O_8$–$NiCl_2$.

$CH_3(CH_2)_3CO_2Me$

(V)

Recently detailed studies have been made of hetero-centred amidyl radicals with an odd electron at the nitrogen atom.[17–19] Methods for the generation of these radicals have been developed based mainly on the homolysis of *N*-halogenoamides,[17,20,21] and some general reactions, *e.g.* intra- and inter-molecular addition to the C=C bond,[18] rearrangement involving a 1,5-H shift, and cyclization into 2-iminotetrahydrofurans [20,22] have been explored. The structure of the ground state of the amidyl radicals has been established by theoretical calculations and e.s.r. spectroscopy.[23] Few studies have been made to date on the reactions of amidyl radicals in systems containing compounds of polyvalent elements.[24]

An investigation of the one-electron oxidation of carboxamides (VIa—c) to the amidyl radicals (VIIa—e) and reactions of the latter with $Na_2S_2O_8$–$CuCl_2$, $Na_2S_2O_8$–NaCl, and $Na_2S_2O_8$–NaCl–NaOH has been made to compare the chemical behaviour of the acyloxyl and amidyl radicals under similar conditions. The oxidative conversion of *NN*-diethylpentanamide (VIf) in the system $Na_2S_2O_8$–$CuCl_2$ has also been studied.

We found that on treatment with equimolar amounts of $Na_2S_2O_8$–$CuCl_2$ and $Na_2S_2O_8$–NaCl (the latter being taken in two-fold excess) in aqueous media at 85—90° (VIa—c) are oxidized to the γ-lactones (IIb—d) and δ-lactones (IIIc, d). A direct one-pot conversion of carboxamides into lactones was not previously known, although γ- and δ-lactones can be produced from amides *via* a number of successive reactions including halogenation of amides into *N*-halogenoamides, followed by photolytic rearrangement into 4- and 5-halogenocarboxamides and cyclization of the latter on treatment with alkali.[20,22]

Under the lactonization reaction conditions amides (VIa—c) also undergo hydrolysis to produce the corresponding alkanoic acids (Ib—d) (Table 3).

Thus, for the two systems investigated, $Na_2S_2O_8$–$CuCl_2$ and $Na_2S_2O_8$–NaCl, amide (VIa) undergoes regiospecific conversion into γ-valerolactone (IIb) and amides (VIb and c) produce a mixture of γ-lactones (IIc and d) and δ-lactones

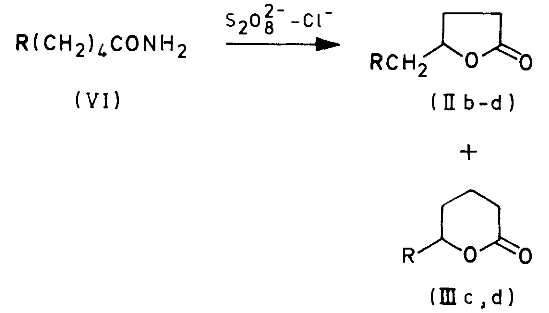
$$\underset{\text{(VIa-e)}}{R^1CH_2CH_2CH_2CH_2CONHR^2} \xrightarrow{S_2O_8^{2-}-Cl^-} \underset{\text{(VIIa-e)}}{R^1CH_2CH_2CH_2CH_2C(O)\dot{N}R^2}$$

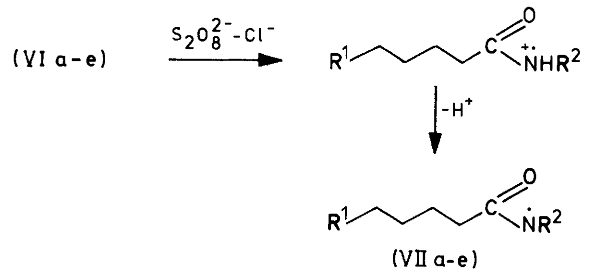
a ; $R^1 = R^2 = H$
b ; $R^1 = Me, R^2 = H$
c ; $R^1 = Et, R^2 = H$
d ; $R^1 = H, R^2 = Me$
e ; $R^1 = H, R^2 = Et$

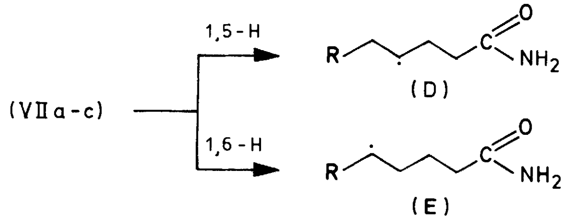
Table 3. Oxidation of alkanamides (VIa—e) by $Na_2S_2O_8$–$CuCl_2$ and $Na_2S_2O_8$–NaCl *

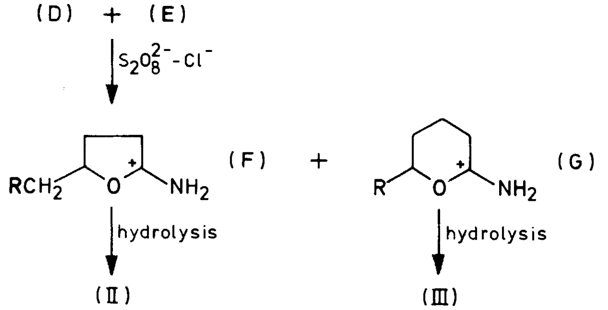
	$Na_2S_2O_8$–$CuCl_2$				$Na_2S_2O_8$–NaCl			
		Reaction products, yield (%) based on the amide converted				Reaction products, yield (%) based on the amide converted		
Substrate	Conversion (%)	γ-Lactone	δ-Lactone	Acid	Conversion (%)	γ-Lactone	δ-Lactone	Acid
(VIa)	98	(IIb), 45		(Ib), 55	80	(IIb), 42		(Ib), 45
(VIb)	90	(IIc), 30	(IIIc), 15	(Ic), 50	68	(IIc), 40	(IIIc), 19	(Ic), 41
(VIc)	92	(IId), 22	(IIId), 15	(Id), 50				
(VId)	60	(IIb), 2		(Ia), 90				
(VIe)	48	(IIb), 6		(Ia), 83				

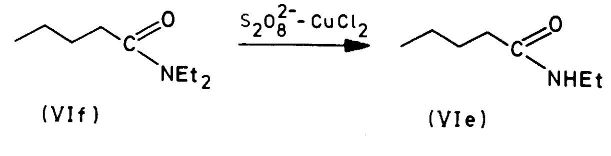
* 85—90°, 10 h; 50 mmol (VI), 50 mmol $Na_2S_2O_8$, 50 mmol $CuCl_2 \cdot 2H_2O$ or 100 mmol NaCl, 150 ml water.











$$\text{(VIa-c)} \xrightarrow{Na_2S_2O_8-NaCl-NaOH} RCH_2CH_2CH_2CH_2NH_2$$

(VIIIa-c)

a; R = H

b; R = Me

c; R = Et

(IIIc and d) with a considerable predominance of the γ-species. The total yield of the lactonization products in the system $Na_2S_2O_8$–$CuCl_2$ is 40%, it being independent of the length of the alkyl group in the primary amides (VIa—c).

The oxidative lactonization of monoalkylamides (VId and e) proceeds only moderately, the yield of (IIb) being 2—6%.

The mechanism of the lactone formation is assumed to involve a one-electron oxidation of amides (VIa—e) to amidyl radicals (VIIa—e) by means of $Na_2S_2O_8$–Cl^- (*cf.* ref. 24). The primary radicals (VIIa—c) are rearranged by 1,5- and 1,6-H shifts into the 3- and 4-carboxamidoalkyl radicals (D) and (E). As a result of the homolytic cyclization of (D) and (E) which proceeds *via* addition to the C=O group followed by oxidation (*cf.* ref. 25), the intermediate cations (F) and (G) are obtained. The immediate hydrolysis thereof under the reaction conditions affords γ-lactones (II) and δ-lactones (III) thus ensuring a one-pot pathway for amide lactonization.

Lactones (II) and (III) can also be obtained in the oxidation of radicals (D) and (E) in the course of heterolytic cyclization of the resulting carbonium ions or chloroalkanamides.

The rearrangement of the more oxidizable, as compared with the primary radicals (VIIa—c), secondary *N*-alkylamidyl radicals (VIId and e) into carboxamidoalkyl radicals is less favourable thermodynamically, and this is responsible for the low yield of γ-lactone (IIb) from the *N*-alkylamides (VId and e). The inertness of (VId and e) towards oxidative lactonization under the reaction conditions studied disagrees with the literature data for the high tendency of *N*-chloro-*N*-methylvaleramide to be converted into γ-valerolactone in non-aqueous media.[23]

The ratio of lactones (II) : (III) in the amide reaction differs substantially from that observed for the corresponding alkanoic acids. No CO_2, a product of oxidative decarboxylation of alkanoic acids in the presence of $Na_2S_2O_8$,[3,8] has been detected in the reaction studied. This enables us to exclude the possibility of the formation of lactones (II) and (III) by hydrolysis of (VI) into acids (I) and lactonization of the latter under the reaction conditions. It has been shown by a check experiment that (VIa) is stable in the system $NaHSO_4$–$CuCl_2$ (see Experimental section) and, thus, acids (I) are obtained as a result of the oxidative hydrolysis of amides (VI).

Comparison of data on the oxidative cyclization of alkanoic acids (Ic and d) and that of the corresponding amides (VIb and c) by $Na_2S_2O_8$–$CuCl_2$ leading to γ- and δ-lactones (Tables 1 and 3) indicates that the regioselectivity of acid lactonization, as judged by the (II) : (III) ratio, is usually higher than that of the corresponding amides, it being *ca.* 1.5 times higher for the pairs (Ic)–(VIb) and (Id)–(VIc). Intramolecular rearrangements of alkylaminyl radicals involving 1,5- and 1,6-H shifts are known to be characterized by a lower regioselectivity than those of alkoxyl radicals.[17] A similar feature seems to be typical of the intramolecular rearrangements of amidyl and acyloxyl radicals, appearing as a reduced regioselectivity of the oxidative lactonization of the former.

Under the action of $Na_2S_2O_8$–$CuCl_2$ *NN*-diethylpentanamide (VIf) undergoes de-ethylation to produce *N*-ethylpentanamide (VIe). No lactone (IIb) was detected in the oxidation products from (VIf).

The addition of NaOH to $Na_2S_2O_8$–NaCl causes a drastic change in the nature of the oxidative conversions of amides (VI) and they undergo conversion into primary amines (VIII) with loss of one carbon atom. Under the reaction conditions amides (VIa—c) are hydrolysed into acids (Ib—d) similarly to their behaviour in the systems $Na_2S_2O_8$–$CuCl_2$ and $Na_2S_2O_8$–NaCl (Table 4).

The most probable mechanism for the formation of amines (VIIIa—c) appears to be that involving the oxidation of amides (VIa—c) or amidyl radicals (VIIa—c) to *N*-chloroamides, their dehydrochlorination into nitrenes (IXa—c) and a Hoffmann-type rearrangement of the latter[26] to produce

Table 4. Oxidation of amides (VIa—c) by $Na_2S_2O_8$-NaCl-NaOH *

Substrate	Conversion (%)	Reaction products, yield (%) based on the amide converted Amine	Acid
(VIa)	100	(VIIIa), 30	(Ib), 55
(VIb)	100	(VIIIb), 36	(Ic), 56
(VIc)	100	(VIIIc), 35	(Id), 49

* 85—90°, 7 h; 50 mmol (VI), 50 mmol $Na_2S_2O_8$, 100 mmol NaCl, 100 mmol NaOH, 200 ml water.

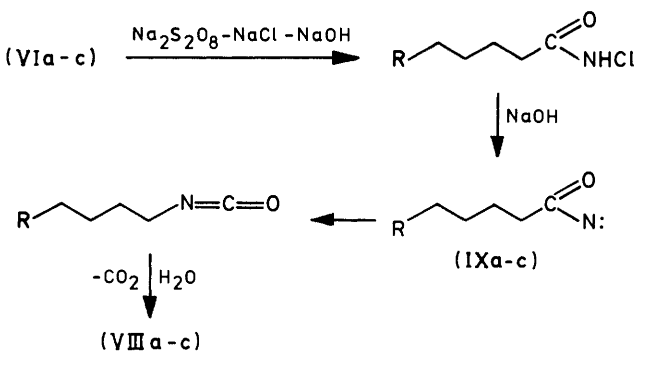
(VIIIa—c). Thus the introduction of NaOH into oxidative system $Na_2S_2O_8$–NaCl has made it possible to interrupt the homolytic reaction pathway for amides (VI) in favour of a carbenoid one (Scheme 3).

Experimental

G.l.c. analyses were carried out on an LKhM-8MD chromatograph fitted with a flame-ionization detector. Columns used were 3 000 × 3 mm with 10% Carbowax 20M treated with H_3PO_4[27] on Celite 545 (52—60 mesh); 1 700 × 3 mm with 3% PEGS on Chromosorb G treated with dimethyldichlorosilane; and 2 000 × 4 mm with 10% Carbowax 20M treated with Na_3PO_4 on Celite 545 (52—60 mesh). ^{1}H N.m.r. spectra were run for solutions in CD_3CN and CCl_4 and recorded with a Tesla BS-497 spectrometer (100 MHz) with hexamethyldisiloxane as internal standard. Mass spectra were obtained with a Varian-MAT CH-6 instrument with a direct inlet system and an ionizing voltage of 70 eV. I.r. spectra were obtained with a Perkin-Elmer 577 spectrometer for thin layers and CCl_4 solutions. G.l.c.–m.s. was carried out on a Varian-MAT CH-111 instrument with a chromatographic inlet an ionizing voltage of 70 eV.

$Na_2S_2O_8$ was a commercially available analytical grade sample; $CuCl_2$, NaCl, NaOH, $FeCl_2$, $FeSO_4$, $FeCl_3$, $CoCl_2$, $NiCl_2$, $Ce_2(SO_4)_3$, NaCl, and $KMnO_4$ were commercially available reagent grade samples used. without additional purification. Alkanoic acids (Ia—g), commercially available reagent grade samples, were purified by distillation *in vacuo*. Amides (VIa—c) were obtained by reaction of the corresponding alkanoyl chlorides with NH_4OH[28] and purified by recrystallization from ethanol, (VIa) m.p. 104—105° (lit.,[29] 106°); (VIb) m.p. 100—100.5° (lit.,[29] 101°); and (VIc) m.p. 96.5° (lit.,[29] 98—98.5°). The interaction of valeroyl chloride with CH_3NH_2, $C_2H_5NH_2$, or $(C_2H_5)_2NH$[28] produced (VId—f) purified by distillation *in vacuo*; (VId) b.p. 150° at 75 mmHg (lit.,[30] 169° at 90 mmHg); (VIe) b.p. 125° at 10 mmHg (lit.[31] 113—115° at 7 mmHg); (VIf) b.p. 108—110° at 18 mmHg (lit.,[32] 94—95° at 10 mmHg). The spectral data of amides (VId—f) are summarized in Table 5.

Oxidation of Alkanoic Acids (Ia—g).—A solution of $Na_2S_2O_8$ (100 mmol) in water (50 ml) was added dropwise at 85—90° for 0.5—1 h to a vigorously stirred mixture of alkanoic acid (100 mmol) and other components (see Tables 1 and 2) in water (90 ml). The mixture was heated at the same temperature for 4—4.5 h with vigorous stirring. On cooling the mixture was extracted with ether (3 × 100 ml). The extract was dried ($MgSO_4$), the ether evaporated, and the residue was analysed by g.l.c., using propionic acid as standard. To isolate lactones (II) and (III), the residue was neutralized with a saturated solution of Na_2CO_3, extracted with ether, dried ($MgSO_4$), the ether evaporated, and the residue distilled *in vacuo*. The yields of lactones (II) and (III) as well as the conversion of acids (I) are summarized in Table 1. The properties and spectral data of the products are summarized in Table 5.



Scheme 3.

CO_2 was measured by taking it up in a flow of argon into two U-tubes filled with Ascarite (CO_2 absorbent). Yields of (II) and (III) and conversion of (I) were the same as in the experiments conducted in a non-inert atmosphere.

Reaction of Methyl Valerate (V) *with* $Na_2S_2O_8$–$CuCl_2$.—To a mixture of (V) (100 mmol) and $CuCl\cdot 2H_2O$ (100 mmol) in water (90 ml) at 85—90° for 0.5 h, was added a solution of $Na_2S_2O_8$ (100 mmol) in water (50 ml). The mixture was heated at the same temperature for 1.5 h with vigorous stirring, cooled, extracted with ether (3 × 100 ml), dried ($MgSO_4$), and the ether evaporated. Ester (V) (92 mmol) was found in the residue by g.l.c.

Oxidation of (Ib) *by the System* $Na_2S_2O_8$–$NiCl_2$.—A solution of $Na_2S_2O_8$ (100 mmol) in water (50 ml) was added dropwise at 85—90° for 1 h to a mixture of (Ib) (100 mmol) and $NiCl_2$ (100 mmol) in water (90 ml). The mixture was heated at the same temperature for 4—4.5 h with vigorous stirring, cooled, treated with a saturated solution of Na_2CO_3 to pH 9, and extracted on cooling with ether (3 × 100 ml). The extract was dried ($MgSO_4$), the ether evaporated and γ-valerolactone (IIb) estimated by g.l.c. The aqueous phase was acidified to pH 3—4 and extracted with ether (3 × 50 ml). The extract was dried ($MgSO_4$) and the ether evaporated. The residue was distilled *in vacuo* to isolate 3- and 5-chlorovaleric acids (IVa and b).

Interaction of (Ib) *with* $KMnO_4$–NaOH.—To a mixture of (Ib) (100 mmol) and NaOH (120 mmol) in water (150 ml), a solution of $KMnO_4$ (100 mmol) in water (100 ml), was added dropwise at 85—90° for 1 h with vigorous stirring. The mixture was heated at the same temperature for 5 h, cooled, treated with Na_2SO_3 until the solution became colourless, acidified to pH 3—4 with diluted H_2SO_4, and extracted with ether (3 × 100 ml). The extract was dried ($MgSO_4$) and the ether evaporated. The residue was analysed by g.l.c. and spectral methods. Acid (Ib) (95 mmol) was recovered.

Oxidation of Alkanamides (VIa—c) *in* $Na_2S_2O_8$–$CuCl_2$ *and* $Na_2S_2O_8$–NaCl.—To a mixture of amides (VIa—c) (50 mmol) and $CuCl_2$ (50 mmol) or NaCl (100 mmol) in water (100 ml), a solution of $Na_2S_2O_8$ (50 mmol) in water (50 ml) was added dropwise at 85—90° for 2.5—3 h with vigorous stirring. The mixture was stirred at the same temperature for another 7 h and cooled down. The residue was filtered off and washed with cold water and a small amount of ether. The residue was found to be unchanged amide (VI). The filtrate was extracted with ether (3 × 100 ml) and chloroform (2 × 100 ml). The extract was dried ($MgSO_4$) and evaporated. The residue was examined by g.l.c. using an acid with one less methylene group

Table 5. Physico-chemical properties and spectral characteristics of lactones (II), (III), acids (IV), and amides (VI)

Compd.	B.p. (°C) (*p*/mmHg)	I.r. spectra (ν/cm^{-1})	^{1}H Chemical shifts (δ)	Mass spectra (*m*/*z*, rel. intensity)	Formula	Found (required) (%)	
						C	H
(IIa)	100 (27)	1 780	2.10 (m, 2 H, $CH_2C\mathit{H}_2CH_2$) 2.35 (t, 2 H, CH_2CO) 4.28 (t, 2 H, CH_2O)	—	$C_4H_6O_2$	55.7 (55.8)	6.9 (7.0)
(IIb)	105—107 (26)	1 780	1.25 (d, 3 H, CH_3) 2.25 (m, 4 H, CH_2CH_2) 4.50 (m, 1 H, CHO)	Similar to ref. 33	$C_5H_8O_2$	59.55 (60.0)	7.7 (8.0)
(IIc)	102—104 (20)	1 770	1.10 (t, 3 H, CH_3) 1.70 (m, 2 H, $CH_2C\mathit{H}_2CH$) 2.25 (m, 4 H, CH_2CH_2) 4.50 (m, 1 H, CHO)	Same	$C_6H_{10}O_2$	62.5 (63.15)	8.6 (8.6)
(IId)	109 (16)	1 770	1.05 (t, 3 H, CH_3) 1.65 (m, 4 H, $CH_3C\mathit{H}_2C\mathit{H}_2$) 2.26 (m, 4 H, CH_2CH_2) 4.50 (m, 1 H, CHO)	Same	$C_7H_{12}O_2$	65.15 (65.6)	9.15 (9.45)
(IIe)	115 (36)	1 780	1.17 (d, 3 H, CH_3) 2.05 (d) and 2.43 (d,) 2 H, CH_2CO) 2.55 (m, 1 H, CH) 3.75 (m) and 2.22 (m, 2 H, CH_2O)	41 (100), 42 (95), 55 (20), 56 (65), 39 (50), 57 (7,) 100 (M^+, 7), 85 (2),	$C_5H_8O_2$	59.65 (60.0)	7.85 (8.0)
(IIf)	104 (10)	1 775	0.90 (t, 6 H, CH_3) 1.25—1.8 (m, 10 H) 2.40 (t, 2 H, CH_2CO)	29 (100), 41 (95), 47 (90), 113 (90), 55 (86), 43 (40), 141 (40), 56 (35), 85 (25), 69 (25)	$C_{10}H_{18}O_2$	70.3 (70.6)	10.45 (10.55)
(IIIb)		1 730		Similar to ref. 33			
(IIIc)		1 725		Same			
(IIId)		1 730		Same			
(IVb)	143—145 (15)	790, 1 710	1.08 (t, 3 H, CH_3) 2.05 (m, 2 H, CH_3CH_2) 4.10 (m, 1 H, CHCl)	60 (100), 42 (75), 41 (70), 55 (65), 56 (60), 43 (60), 73 (30), 100 (20)	$C_5H_9ClO_2$	43.8 (43.95)	6.5 (6.6)
(IVa)	149—152 (13)	790, 1 710	2.00 (d, 4 H, CH_2CH_2) 3.60 (t, 2 H, CH_2Cl) 2.30 (t, 2 H, CH_2CO)	73 (100), 55 (90), 41 (80), 43 (70), 60 (70), 56 (60), 100 (60), 54 (50), 42 (50)	$C_5H_9ClO_2$	43.8 (43.95)	6.5 (6.6)
(VId)	150 (75)	1 640, 3 070, 3 350	0.90 (t, 3 H, CH_3CH_2) 1.50 (m, 4 H, CH_2CH_2) 2.20 (t, 2 H, CH_2CO) 2.60 (s, 3 H, CH_3N) 7.25 (s, 1 H, NH)	73 (100), 55 (90), 41 (80), 43 (80), 60 (60), 54 (50), 56 (50), 100 (40), 83 (20)			
(VIe)	125 (10)	1 640, 3 070, 3 340	0.92 (t, 3 H, $CH_3CH_2CH_2$) 1.24 (m, 3 H, CH_3CH_2N) 1.60 (m, 4 H, $CH_3CH_2CH_2$) 2.23 (t, 2 H, CH_2CO) 3.31 (q, 2 H, CH_2N) 5.8 (s, 1 H, NH)	87 (100), 72 (80), 44 (40), 57 (25), 41 (21), 100 (20), 85 (15), 114 (10), 129 (M^+, 7), 128 (6)			
(VIf)	108—110 (8)	1 640	0.9 (t, 3 H, $CH_3CH_2CH_2$) 1.24 (m, CH_3CH_2N, 6 H) 2.62 (m, 4 H, $CH_3C\mathit{H}_2CH_2$) 2.20 (t, 2 H, CH_2CO) 3.24 (q, 4 H, CH_2N)	58 (100), 44 (90), 41 (70), 57 (60), 72 (50), 56 (40), 46 (40), 100 (40), 115 (60), 128 (30), 157 (M^+, 10)			

as standard for the identification of lactones and acids. To determine the amide recovered in the residue, the lower homologue of the amide was used as standard.

To isolate lactones (II) and (III), the residue was neutralized with a saturated solution of Na_2CO_3, extracted with ether (3 × 100 ml), dried ($MgSO_4$), the ether evaporated, and the residue distilled *in vacuo*. The properties and spectral data of lactones (IIb—d) and (IIIc, d) are listed in Table 5.

Oxidation of the N-*Substituted Valeramides* (VId—f) *in* $Na_2S_2O_8$—$CuCl_2$.—To a mixture of (VId—f) (100 mmol) and $CuCl_2$ (100 mmol) in water (150 ml), a solution of $Na_2S_2O_8$ (100 mmol) in water (100 ml) was added at 85—90° for 2 h with vigorous stirring. The mixture was stirred at the same temperature for 7 h and extracted with ether on cooling. The extract was dried ($MgSO_4$) and the ether evaporated. The residue was fractionated *in vacuo*.

Attempted Hydrolysis of (VIa) *in* $NaHSO_4$-$CuCl_2$.—A mixture of (VIa) (100 mmol), $NaHSO_4$ (200 mmol), and $CuCl_2$ (100 mmol) in water (250 ml) was heated at 85—90° for 10 h with vigorous stirring. On cooling the mixture was extracted with ether (3 × 100 ml). The extract was dried ($MgSO_4$) and evaporated. The residue contained the recovered (VIa) (98 mmol).

Oxidation of Alkanamides (VIa—c) *in* $Na_2S_2O_8$-NaCl-NaOH.—To a mixture of (VIa—c) (50 mmol) and NaCl (100 mmol) in water (100 ml) were added dropwise at 85—90° for 2 h with stirring from two funnels solutions of $Na_2S_2O_8$ (50 mmol) and NaOH (100 mmol) in water (50 ml), the NaOH solution being added at a rate twice that of the $Na_2S_2O_8$ solution. The mixture was heated at the same temperature for another 5 h and on cooling it was extracted with ether. The extract was dried ($MgSO_4$) and the ether evaporated *in vacuo*. Amines (IIIa—c) were isolated by distillation. Their physical constants and spectral data are identical with those of the known samples. The aqueous layer was acidified with 1N-HCl to pH 3—4 and extracted with ether (3 × 100 ml). The extract was dried ($MgSO_4$) and the ether evaporated. Distillation *in vacuo* produced alkanoic acids (Ib—d) identical to the known samples.

References

1 D. I. Davies and M. J. Parrott, ‘Free Radicals in Organic Synthesis,’ Springer-Verlag, Berlin-Heidelberg-New York, 1978.

2 W. Parkev, J. S. Roberts, and R. Ramage, *Quart. Rev.*, 1967, **21**, 331.

3 G. I. Nikishin, E. I. Troyansky, and I. V. Svitanko, *Izv. AN SSSR, Ser. Khim.*, 1981, 1436.

4 G. I. Nikishin, E. I. Troyansky, and I. V. Svitanko, *Izv. AN SSSR, Ser. Khim.*, 1980, 2184.

5 J. D. Bacha and J. K. Kochi, *Tetrahedron*, 1968, **24**, 2215.

6 J. M. Anderson and J. K. Kochi, *J. Org. Chem.*, 1970, **35**, 986.

7 S. S. Lande and J. K. Kochi, *J. Am. Chem. Soc.*, 1968, **90**, 5196.

8 Yu. N. Ogibin, L. Kh. Rakhmatullina, and G. I. Nikishin, *Izv. AN SSSR, Ser. Khim.*, 1975, 2723; J. M. Anderson and J. K. Kochi, *J. Am. Chem. Soc.*, 1970, **92**, 1651.

9 Yu. N. Ogibin, E. I. Troyansky, G. I. Nikishin, V. I. Kadentsev, E. D. Lubuzh, and O. S. Chizhov, *Izv. AN SSSR, Ser. Khim.*, 1976, 2518.

10 C. J. Myall, D. Pletcher, and C. Z. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1976, 2035.

11 J. Kenyon and M. C. R. Symons, *J. Chem. Soc.*, 1953, 2129, 3580.

12 Yu. N. Ogibin, E. I. Troyansky, V. I. Kadentsev, E. D. Lubuzh, O. S. Chizhov, and G. I. Nikishin, *Izv. AN SSSR, Ser. Khim.*, 1974, 2522.

13 D. P. N. Satchell and R. S. Satchell, ‘Substitution in the Groups COOH and COOR,’ in, ‘The Chemistry of Carboxylic Acids and Esters,’ ed. S. Patai, Interscience, New York, 1969, pp. 375—452.

14 Yu. N. Ogibin, E. I. Troyansky, and G. I. Nikishin, *Izv. AN SSSR, Ser. Khim.*, 1974, 2239.

15 G. A. Russel, in, ‘Free Radicals,’ ed. J. K. Kochi, Interscience, New York, 1973, vol. 1, p. 275.

16 R. Kh. Freidlina and A. B. Terent'ev, *Acc. Chem. Res.*, 1977, **10**, 9.

17 R. S. Neale, *Synthesis*, 1971, **1**. 1.

18 S. A. Glover and A. Goosen, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1348.

19 M. E. Kuehne and D. A. Horne, *J. Org. Chem.*, 1975, **40**, 1287.

20 D. H. R. Barton, A. L. J. Beckwith, and A. Goosen, *J. Chem. Soc.*, 1965, 181.

21 P. Mackiewicz, R. Furstoss, B. Waegell, R. Cote, and J. Lessard, *J. Org. Chem.*, 1978, **43**, 3746.

22 R. S. Neale, N. L. Marcus, and R. G. Scheppers, *J. Am. Chem. Soc.*, 1966, **88**, 3051.

23 T. Koenig, J. A. Hoobler, C. E. Klopfenstein, G. Hedden, F. Sunderman, and B. R. Russel, *J. Am. Chem. Soc.*, 1974, **96**, 4573.

24 A. R. Forrester, A. S. Ingram, and R. H. Thomson, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2847.

25 Yu. N. Ogibin, E. I. Troyansky, V. I. Kadentsev, E. D. Lubuzh, O. S. Chizhov, and G. I. Nikishin, *Izv. AN SSSR, Ser. Khim.*, 1981, 1070.

26 P. Kovacic and M. K. Lowery, *Chem. Rev.*, 1970, **70**, 639.

27 B. E. Nadin, *Zh. Anal. Khim.*, 1978, **88**, 836.

28 Weigand-Hilgetag, ‘Organisch-Chemische Experimentierkunst,’ Johann Ambrosius Barth Verlag, Leipzig, 1970, pp. 477, 479.

29 G. E. Philbrook, *J. Org. Chem.*, 1954, **19**, 623.

30 C. F. D'Amelio and E. E. Reid, *J. Am. Chem. Soc.*, 1937, **59**, 109.

31 Yu. K. Yuryev, Z. V. Belyakova, P. V. Kostetsky, and A. I. Prokofyev, *Zh. Obshch. Khim.*, 1959, **29**, 2594.

32 Yu. K. Yuryev and Z. V. Belyakova, *Zh. Obshch. Khim.*, 1958, **28**, 3.

33 E. Honkanen, J. Moisio, and P. Karvonen, *Acta Chem. Scand.*, 1965, **19**, 370.

Received 6th *July* 1982; *Paper* 2/1140