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NUCLEOPHILIC CHARACTER OF ALKYL RADICALS—V

SELECTIVE HOMOLYTIC α-OXYALKYLATION OF HETEROAROMATIC BASES*

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Abstract—The direct introduction of α-oxyalkyl groups into heteroaromatic bases has been achieved by means of various oxidising agents: hydrogen peroxide, t-butyl-hydroperoxide, ammonium peroxydisulphate, sodium perborate and bis-(4-t-butylcyclohexyl)-peroxydicarbonate. The good yields and the complete selectivity obtained are due to the nucleophilic character of the α-oxyalkyl radicals. A quantitative study concerning the nucleophilic character of the dioxanyl radical, carried out by measuring the relative rates of attack on 4-substituted quinolines; revealed in detail all the features of nucleophilic substitutions.

INTRODUCTION

HETEROAROMATIC bases, as electron-deficient substrates, readily react with nucleophilic reagents, and when protonation of the heteroaromatic bases increases the electron-deficient nature their reactivity to nucleophilic reagents is increased. In some instances the nucleophilic agents, cause deprotonation of the base, but as this does not generally occur with nucleophilic radicals, we have taken advantage of the increased nucleophilic reactivity, following protonation, to find new types of homolytic substitution reactions.

Homolytic alkylation.[1] Due to the nucleophilic character of the alkyl radicals and the large variety available, these alkylations have a synthetic and theoretical interest comparable to electrophilic alkylation in the homocyclic series. Analogously, *homolytic acylation*[2] using aldehydes has a considerable interest because of the variety of acyl radicals and heteroaromatic bases to which it is applicable. *Homolytic amidation*[3] with formamide has similar characteristics.

The success obtained in all of these cases induced us to consider other carbon radicals, which potentially could have a nucleophilic character and at the same time be readily available. Thus *homolytic α-amidoalkylation*[4] of heteroaromatic bases using amides has many synthetic applications.

In this paper we describe *homolytic α-oxyalkylation* of heteroaromatic bases using alcohols and ethers. In addition to measuring the relative rates in 4-substituted quinolines, we determined quantitatively the influence of the nucleophilic character of the dioxanyl radical.

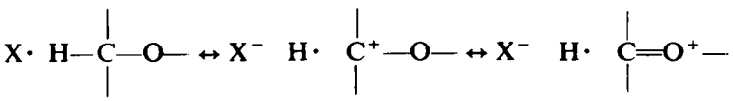
RESULTS AND DISCUSSION

The abstraction of hydrogen from the α position to the oxygen of alcohols and ethers

* Part IV: See Ref. 1c.

occurs frequently and is a readily available source of α-oxyalkyl radicals. Resonance stabilization and polar factors were used to explain the ease of radical attack on these substrates. Recent studies[5] appear to exclude the possibility that the O atom in the α position to the free C-radical may cause a stabilization by resonance.

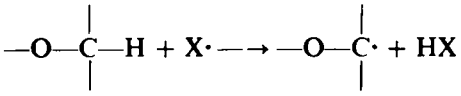
The case of the hydrogen abstraction, determined by polar factors, operates with electrophilic radicals (X·) by contribution of the following polar forms in the transition state:



It is rather a function of the abstraction species than a measure of stability of the intermediate.

This point of view is supported by recent *ab initio* MO studies[6] of the charge density of alcohols and ethers which indicate that the oxygen in these compounds is substantially less negative than in water. This is primarily associated with the back donation of charge from the π type lone pair of the oxygen into the antibonding orbitals of the adjacent C—H groups, thereby causing a higher electron availability and, consequently, a more ready attack by electrophilic radicals; such a charge distribution, long appreciated for substituted unsaturated compounds (vinyl and aromatic ether, phenols) would occur also for saturated groups and could be for instance the primary cause of the low dipole moments of ethers.[6]

The α-oxyalkyl radicals used in this study were prepared by oxidation of alcohols and ethers with a wide variety of electrophilic radicals generated thermally or by redox systems;



the radical sources used were hydrogen peroxide, t-butyl-hydroperoxide, ammonium peroxydisulphate, sodium perborate and bis-(4-t-butylcyclohexyl)-peroxydicarbonate.

Despite the well known ease with which the α-oxyalkyl radicals are oxidized, when the reaction is carried out in the presence of a protonated hereroaromatic base, the radicals attack the base producing the corresponding substitution products.

Often these reactions are very clean; the yields based on the converted base are generally quantitative: the selectivity in the α and γ positions to the heterocyclic nitrogen is complete; the experimental conditions are simple (the reactions are carried out in aqueous solutions at a moderate temperature). Also in view of the ready availability of most of the reagents used, there is a certain synthetic interest.

If more than one reactive position is free, mono- and di-substituted products can be obtained depending on the degree of conversion of the heteroaromatic base. In fact the first group to enter does not appreciably affect the reactivity of the heteroaromatic derivative.

The results obtained with a series of ethers and heteroaromatic bases are shown in Table 1.

In the case of cyclic ethers, the oxyalkyl radical attacks the heterocyclic substrate without undergoing β-scission, and for this reason the reaction is of synthetic interest.

1,3-Dioxolane is selectively attacked by the t-But-O· radical forming a 4-substituted

TABLE 1. REACTION OF HETEROAROMATIC BASES WITH α-OXYLKYLRADICALS GENERATED FROM ETHERS

Base	Ether	Radical source*	Product	Yield %†	Other products
4-CN-pyridine	dioxane	*c*	2-dioxanyl-4-CN-pyridine	65	8% of 2,6-di-derivative
2-Me-quinoline	dioxane	*a*	4-dioxanyl-2-Me-quinoline	48	
2-Me-quinoline	dioxane	*c*	4-dioxanyl-2-Me-quinoline	74	
4-Me-quinoline	dioxane	*a*	2-dioxanyl-4-Me-quinoline	54	
4-Me-quinoline	dioxane	*c*	2-dioxanyl-4-Me-quinoline	68	
4-OMe-quinoline	dioxane	*a*	2-dioxanyl-4-OMe-quinoline	35	
4-Cl-quinoline	dioxane	*a*	2-dioxanyl-4-Cl-quinoline	42	
4-CN-quinoline	dioxane	*a*	2-dioxanyl-4-CN-quinoline	55	
Benzothiazole	dioxane	*a*	2-dioxanyl-benzothiazole	40	
Pyrazine	dioxane	*a* or *b*	2-dioxanyl-pyrazine	~38	~20% of (III); ~10% of (V)
Isoquinoline	dioxane	*c*	1-dioxanyl-isoquinoline	28	
Quinoxaline	dioxane	*a* or *b*	2-dioxanyl-quinoxaline	~50	~6% of 2,3-di-derivative
Quinoxaline	tetrahydrofurane	*a*	2-(tetrahydrofuran-2-yl)-quinoxaline	52	
Quinoxaline	1,3-dioxolane	*a*	2-(dioxolan-4-yl)-quinoxaline (I)	35	
Quinoxaline	1,3-dioxolane	*c*	2-(dioxolan-4-yl)-quinoxaline (I)	45	25% of (II)
Quinoxaline	ethyl–ether	*a*	2-(1-ethoxy-ethyl)-quinoxaline	26	10% of 2-Ac-derivative 12% of 2-Et-derivative

* [a] t-but-OOH + Fe^{++}; [b] H_2O_2 + Fe^{++}; [c] $(NH_4)_2S_2O_8$ at 80–90°.

† Based on the heteroaromatic base.

TABLE 2. REACTION OF HETEROAROMATIC BASES WITH α-OXYALKYL RADICALS GENERATED FROM ALCOHOLS

Base	(mole)	Alcohol	Radical source	(mole)	Product	Yield %*
2-CH_3-quinoline	(1)	MeOH	$(NH_4)_2S_2O_8$	(2)	4-CH_2OH-2-CH_3-quinoline	86
2-CH_3-quinoline	(1)	MeOH	$NaBO_3$	(2)	4-CH_2OH-2-CH_3-quinoline	60
2-CH_3-quinoline	(1)	MeOH	peroxydicarbonate	(1)	4-CH_2OH-2-CH_3-quinoline	45
2-CH_3-quinoline	(1)	MeOH	$H_2O_2 + Cr^{++}$	(1)	4-CH_2OH-2-CH_3-quinoline	12
2-CH_3-quinoline	(1)	MeOH	$NaBO_3 + Fe^{++}$	(2)	4-CH_2OH-2-CH_3-quinoline	30
2-CH_3-quinoline	(1)	MeOH	$(NH_4)_2S_2O_8 + Na_2SO_3$	(4)	4-CH_2OH-2-CH_3-quinoline	40
2-CH_3-quinoline	(1)	EtOH	percarbonate	(1)	4-hydroxyethyl-2-CH_3-quinoline	22‡
2-CH_3-quinoline	(1)	EtOH	t-but-OOH + Fe^{++}	(1)	4-hydroxyethyl-2-CH_3-quinoline	14
Quinoline	(1)	MeOH	$(NH_4)_2S_2O_8$	(2)	2- and 4-CH_2OH-quinoline	53
Quinoline	(1)	MeOH	t-but-OOH + Fe^{++}	(0·3)	2- and 4-CH_2OH-quinoline	23†
Quinoline	(1)	MeOH	$H_2O_2 + Cr^{++}$	(2)	2- and 4-CH_2OH-quinoline	27
Quinoline	(1)	EtOH	t-but-OOH + Fe^{++}	(2)	2- and 4-hydroxyethylquinoline	25
4-CH_3-quinoline	(1)	MeOH	$(NH_4)_2S_2O_8$	(1)	2-CH_2OH-4-CH_3-quinoline	43
Pyridine	(1)	MeOH	$(NH_4)_2S_2O_8$	(0·2)	2- and 4-CH_2OH-pyridine	40†
Isoquinoline	(1)	MeOH	$(NH_4)_2S_2O_8$	(2)	1,2-di-(1-isoquinolyl)-ethylene glycol	31

* Based on the heteroaromatic base.

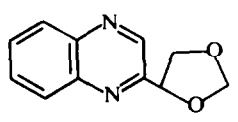
† Based on the oxidant. Yields on the unrecovered starting material are practically quantitative.

‡ Other product: 4-Ac-2-Me-quinoline.

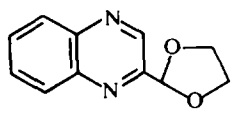
derivative (I), while with the $HO^{\cdot}$ and $SO_4^{\cdot-}$ radicals both the 4- and 2-substituted (II) derivatives are obtained.

Some di-oxyalkyl derivatives were present if the heteroaromatic substrata had more than one reactive position.

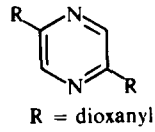
In the reaction between pyrazine and dioxane, mono- and di-derivatives (III) were produced, as well as the dimer (V), thus again supporting the homolytic nature of the reaction which occurred via dimerization of the intermediate radical (IV) and subsequent oxidation



I

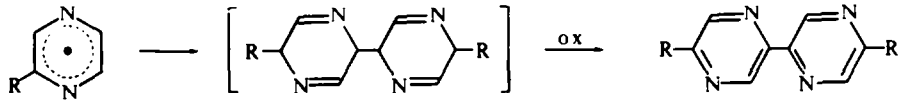


II



R = dioxanyl

III



IV V

The acyclic ethers undergo a partial β-scission with the formation of carbonyl and alkyl compounds. Thus with ethyl ether, introduction of the oxyalkyl group, is accompanied by appreciable quantities of ethyl and acetyl derivatives. The formation of these latter derivatives is attributed to a β-scission of the α-oxylkyl radical:

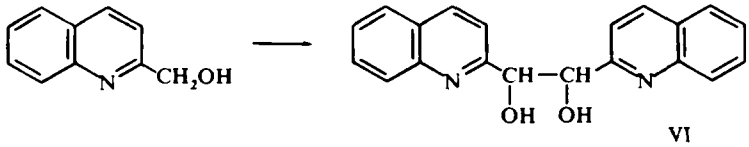
$$CH_3—CH_2—O—CH_2CH_3 \longrightarrow CH_3CHO + CH_3CH_2^{\cdot}$$

the ethyl radical attacks the heteroaromatic base directly and selectively,[1] forming the corresponding ethyl derivative, while acetaldehyde acts as a source of acetyl radicals resulting in homolytic acetylation as recently described.[2]

The results obtained with methanol and ethanol and various heteroaromatic bases are summarized in Table 2.

The yields obtained with methanol are higher than with ethanol; with secondary alcohols, such as isopropanol, the results were not good, probably due to the ease with which the tertiary hydroxyalkyl radical is oxidised to the corresponding ketone.

The hydromethyl group in α-position to the heterocyclic nitrogen is sensitive to atmospheric oxygen and tends to form an oxidative dimer product:



VI

In the hydroxyethylation with ethanol a certain amount of the acetyl derivative is also formed; probably due to the oxidation of the secondary alcohol initially formed

or to the formation of a certain quantity of acetaldehyde which could act as a homolytic acylating agent.[2]

A different homolytic hydroxymethylation of quinoline was described in the decomposition of a methanolic solution of hydroxylamine-O-sulfonic acid.[7]

To study quantitatively the effect of the polar character on the reactivity of the α-oxyalkyl radicals, we determined the relative reaction rates of the dioxanyl radical with 4-substituted quinolines. This radical was selected for practical reasons: the possibility of working in a homogeneous medium (i.e. aqueous solution), and the ease of the qualitative and quantitative analysis of the reaction products. These characteristics were important as the relative reaction rates were determined using the competitive method.

The 4-substituted quinolines are particularly interesting substrates for the study of the polar characteristics of this radical for the following reasons:

(a) No secondary products are formed with all the substituted quinolines used, only dioxyanyl-quinolines were produced;

(b) The reaction is completely selective and only the 2-position of quinoline is attacked in all cases;

(c) The resonance stabilization effects of the substituents are minimized, as the substituents are in the *meta* position with respect to the position of attack by the dioxanyl radical, and so the influence of the polar characters is indicated.

To determine the relative reaction rates the competitive method was used, working with excess of the heterocyclic derivative in an aqueous dioxane solution. Initially the single substrates were studied in order to observe the progress of the reaction. The reaction products were isolated and used to confirm the response of the gas-chromatographic analysis in the competitive experiments. The results are summarized in Table 3.

TABLE 3. RELATIVE RATES IN THE HOMOLYTIC OXYALKYLATION OF 4-X-QUINOLINES WITH DIOXANYL RADICAL

X	k_X/k_H
OCH_3	0·12
CH_3	0·75
H	1
Cl	2·7
$COOC_2H_5$	7·1
CN	22

A Hammett correlation was not observed, mainly due to the fact that the OMe group is deactivating, despite the positive value of its σ_m and chlorine is less active than would be expected from its σ_m constant. This behaviour however supports the nucleophilic character of the dioxanyl radical in that it reproduces even in detail the analogous behaviour of the quinoline ring in a classic nucleophilic substitution reaction: the methoxydechlorination of 4-substituted-2-chloro-quinolines;[8] also in this latter case the substituents in the 4-position exert an influence on the reactivity, that does not correlate with the Hammett constants, in that the OMe group is deactivating and the chlorine is less activating than would be expected. The fact can be explained by an enhanced electron releasing effect, which involves direct interaction

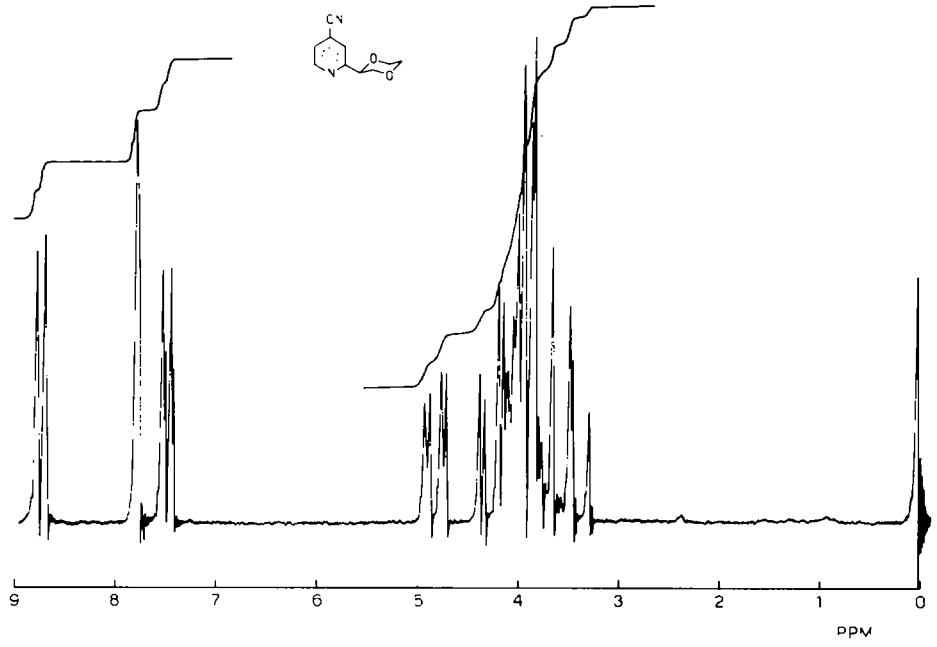


FIG 1A

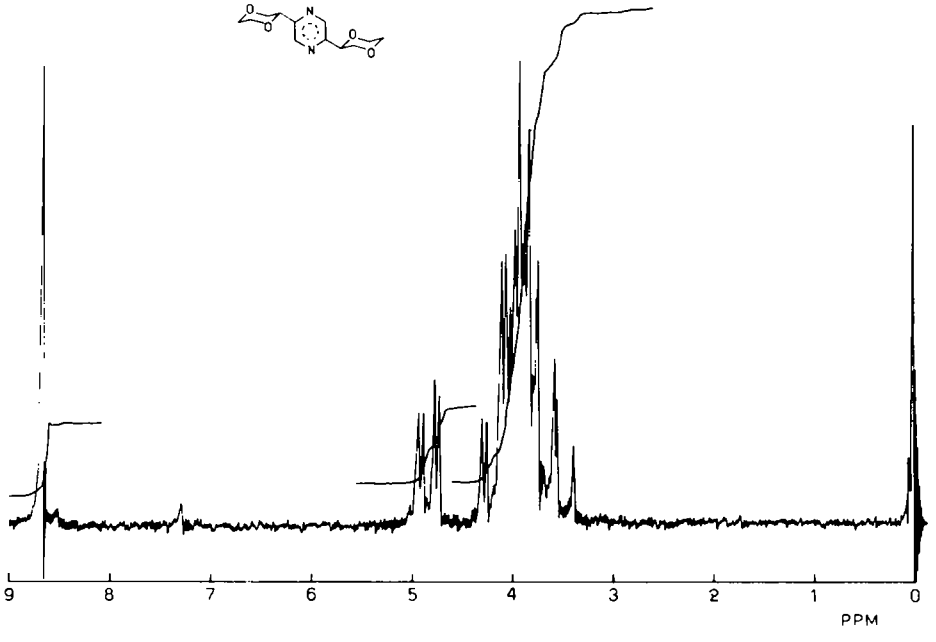


FIG 1B

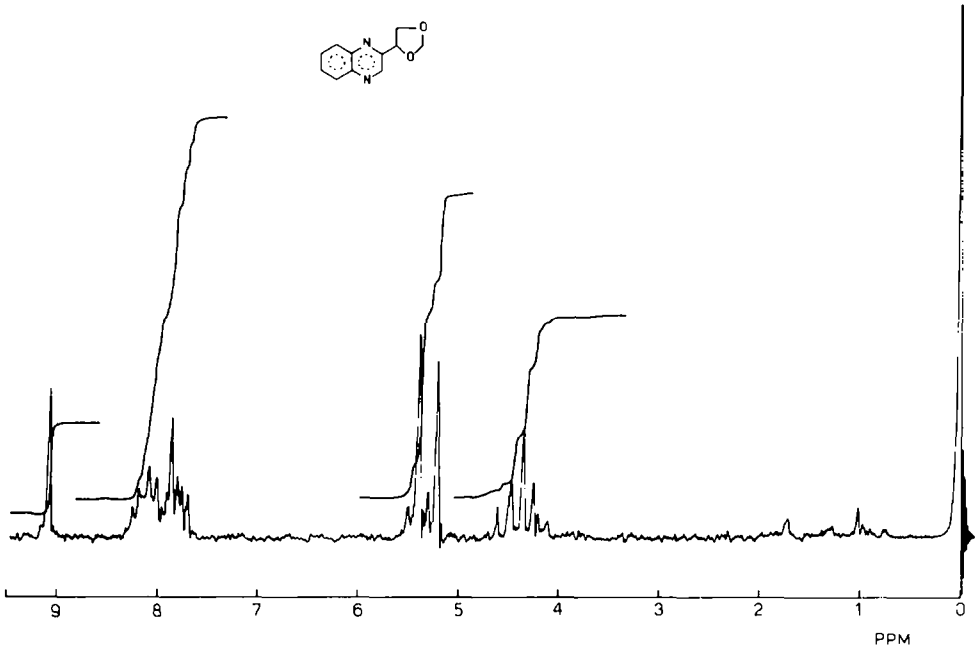


FIG 1C

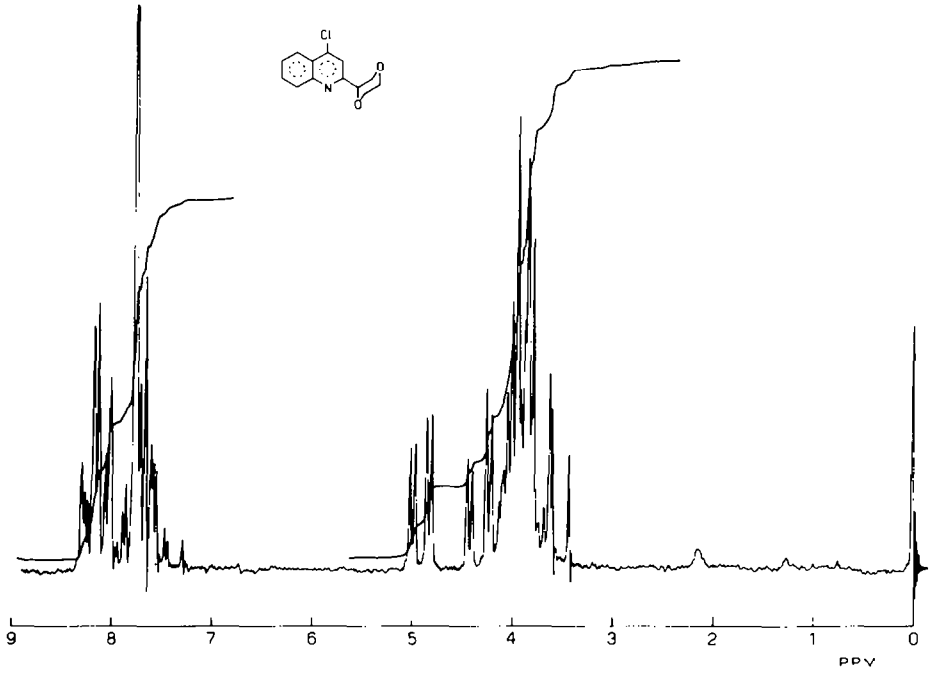
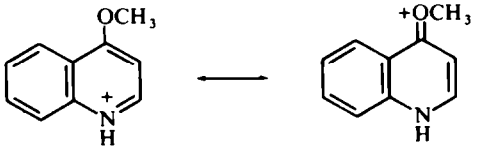


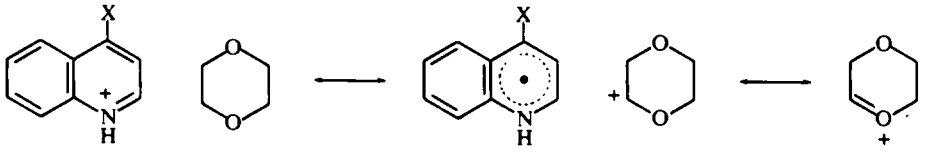
FIG 1D

of the protonated aza-group with the substituent, thereby reducing the electron-accepting capacity of the heteroaromatic ring in the rate determining step of the reaction:

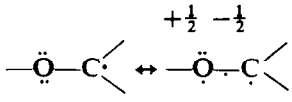


A similar behaviour was also observed in the homolytic methylation of 4-substituted pyridines.[9] It is therefore a general phenomenon, which is peculiar to the pyridine ring towards nucleophilic species (ionic or radical). It is evident that the dioxanyl radical shows a clear nucleophilic character even though the O atom in the β-position has a definite electron-withdrawing effect (in fact the pK_a for piperidine and morpholine are 11·1 and 8·3 respectively). This indicates that the oxygen in the α-position to the C-radical has an electron-releasing effect that counterbalances the inductive electron-withdrawing effects whether of the same or of that in the β-position.

This effect could occur in the ground state of the dioxanyl radical, in a similar way in which MO studies[6] show it for the corresponding saturated derivatives, that is a back donation of charge from the lone pair of O atoms to the α C-radical; therefore an analogous effect would determine both the easy hydrogen abstraction from alcohols and ethers by electrophilic radicals and the nucleophilic character of the α-oxyalkyl radicals. This effect would be accentuated in the transition state for the contribution of the following polar forms:



The nucleophilic character of the α-oxyalkyl radicals can also be rationalized in terms of the Linnett theory:[10]



Measurement of the relative rates with cyclohexyl and α-tetrahydropyranyl radicals are at the present being studied, using 4-substituted quinoline as substrates. so as to have a more direct comparison on the influence that an ether oxygen in the α and β-positions exercises on the polar characteristic of the C-radical.

EXPERIMENTAL

All the reagents used were commercial products. Mps are uncorrected. NMR spectra were recorded on a Varian A-60 spectrometer; chemical shifts are in ppm (δ) from TMS as the internal standard. Mass spectra were obtained on a Hitachi–Perkin–Elmer RMU-6D mass spectrometer operating with an ionization energy of 70 eV.

The ethers as a source of α-oxyalkyl radicals—General procedures

(*a*) A saturated aqueous soln of ferrous sulphate (0·06 mole), and t-butyl-hydroperoxide* (0·06 mole) were separately and simultaneously dropped (15 min) into a well stirred and refrigerated (0–10°) soln of the heterocyclic base (0·02 mole) in 50% H_2SO_4 (0·03 mole), in the presence of the ether (0·4 mole). Only in the case of dioxane the mixture was homogeneous. After the addition, the soln was stirred at 10–20° for 30 min, the pH was adjusted to 8 with sat Na_2CO_3 aq and the mixture extracted with ethyl ether. After preliminary testing by GLC [Varian 1400 Aerograph, flame ionization detector, column (2 m) packed with 5% SE 30 on sylanized Chromosorb W (60–80 mesh), programmed temp 70–280° at 10°/min], the product was isolated by column chromatography (Silicagel Merk, 0·05–0·2 mm), eluting with hexane/EtAc 4:1).

(*b*) 34% H_2O_2 (0·06 mole) was used in the place of the equivalent quantity of t-butyl-hydroperoxide of the previous procedure.

(*c*) A soln of the heterocyclic base (0·02 mole) in 50% H_2SO_4 (0·03 mole) was mixed with a saturated aqueous soln of $(NH_4)_2S_2O_8$ (0·06 mole) and the ether (0·4 mole) was added. The mixture was kept on a water bath at 80–90° for 2 hr, then neutralized with sat Na_2CO_3 aq and extracted with ethyl ether, after evaporating the organic layer at reduced pressure, the residue was chromatographed as in procedure *a*.

The IR spectra of all the products reported in this first section showed a strong band of the C—O stretching lying in the range 1100–1150 cm^{-1}. The pattern of the dioxanyl group in the NMR spectra of all related derivatives very closely resembles to that reported in Fig 1a.

2-*dioxanyl*-4-*cyano-pyridine* was obtained from 4-CN-pyridine by procedure *a*, mp 94° (colourless prisms from light petroleum). (Found: C, 63·23; H, 5·42; N, 14·82. $C_{10}H_{10}N_2O_2$ requires: C, 63·15; H, 5·30; N, 15·07%; NMR ($CDCl_3$): 3·3–4·4 (m, 6H, $C\underline{H}_2$—O—); doublet of doublets center at 4·85 ppm (1H, Ar—$C\underline{H}$—O—); 7·5 (d, 1H, H-5); 7·75 (s, 1H, H-3); 8·7 (d, 1H, H-6). (See Fig 1a). M^+ at *m/e* 190; other peaks at *m/e* 159, 145, 131, 118, 104, 90, 77.

Small quantities of the 2,6-*di-dioxanyl*-4-*cyano-pyridine* were also found. Colourless needles mp 131°. (Found: C, 60·66: H, 5·74; N, 10·14. $C_{14}H_{16}N_2O_4$ requires: C, 60·86; H, 5·84; N, 10·14%); NMR ($CDCl_3$): 3·2–4·4 (m, 12H, —$C\underline{H}_2$—O—); doublet of doublets center at 4·8 (2H, Ar—$C\underline{H}$O—) and 7·7 (s, 2H, H-3 and H-5). M^+ at *m/e* 276; major peaks at *m/e* 217, 187, 173, 159, 146, 130, 104, 73.

2-*Methyl*-4-*dioxanyl-quinoline* was obtained from 2-CH_3-quinoline by procedures *a* and *c*, mp 82° (colourless prisms from light petroleum). (Found: C, 73·50; H, 6·82; N, 6·25. $C_{14}H_{15}NO_2$ requires: C, 73·34; H, 6·59; N, 6·11%). NMR ($CDCl_3$): 2·8 (s, 3H,Me-2); 3·2–4·3 (m, 6H, —$C\underline{H}_2$—O—); doublet of doublets center at 5·4 (1H, Ar—$C\underline{H}$—O—) 7·5 (s, 1H, H-3); 7·3–8·2 ppm (m, 4H, aromatic protons). M^+ at *m/e* 229; major peaks at *m/e* 199, 184, 170, 147, 128, 115, 102, 89, 77.

2-*Dioxanyl*-4-*methyl-quinoline* was obtained from 4-CH_3-quinoline by procedures *a* and *c* as colourless prisms mp 86–87° (light petroleum). (Found: C, 73·40; H, 6·75; N, 6·20. $C_{14}H_{15}NO_2$ requires: C, 73·34; H, 6·59; N, 6·11%). NMR ($CDCl_3$): 2·7 (s, 3H, Me-4); 4·5–5·5 (m, 6H, —$C\underline{H}_2$—O—); doublet of doublets center at 4·9 ppm (1H, Ar—$C\underline{H}$—O—); 7·4 (s, 1H, H-3); 7·3–8·2 ppm (m, 4H, aromatic protons). M^+ at *m/e* 229; major peaks at *m/e* 199, 184, 170, 147, 115, 89, 77.

2-*Dioxanyl*-4-*methoxy-quinoline* was obtained from 4-OCH_3-quinoline by procedure *a* as a white powder, mp 86–87° (ligroine). (Found: C, 68·82; H, 6·16; N, 5·84. $C_{14}H_{15}NO_3$ requires: C, 68·55; H, 6·16; N, 5·58%). NMR ($CDCl_3$): 4·1 (s, 3H, OCH_3); 3·4–4·4 (m, 6H—$C\underline{H}_2$—O—); doublet of doublets center at 4·9 ppm (1H, Ar—$C\underline{H}$—O—); 7·0 (s, 1H, H-3); 7·2–8·2 ppm (m, 4H, aromatic protons). M^+ at *m/e* 245; major peaks at *m/e* 214, 186, 159, 143, 130, 115, 102, 89, 77.

2-*Dioxanyl*-4-*chloro-quinoline* was obtained from 4-Cl-quinoline by procedure *a* as colourless needles, mp 63–64° (ligroine). (Found: C, 62·78; H, 4·97; N, 5·87. $C_{13}H_{12}ClNO_2$ requires: C, 62·53; H, 4·84; N, 5·61%). NMR ($CDCl_3$): 3·4–4·4 (m, 6H, —$C\underline{H}_2$—O—); doublet of doublets center at 4·9 ppm (Ar—$C\underline{H}$—O—); 7·7 (s, 1H, H-3); 7·3–8·3 ppm (m, 4H, aromatic protons). (See Fig 1d). M^+ at *m/e* 249; major peaks at *m/e* 219, 190, 163, 128, 101, 87, 75.

2-*dioxanyl*-4-*cyano-quinoline* was obtained from 4-CN-quinoline by procedure *a* as colourless prisms,

* 75% in di-t-butyl-peroxide

mp 129–130° (ligroine). (Found: C, 70·26; H, 5·23; N, 11·58. $C_{14}H_{12}N_2O_2$ requires: C, 69·98; H, 5·03; N, 11·66%). NMR ($CDCl_3$): 3·4–4·5 (m, 6H, $-C\underline{H}_2-O-$); doublet of doublets center at 5·0 (1H, Ar–$C\underline{H}$(–O–)–); 8·0 (s, 1H, H-3); 7·6–8·3 ppm (m, 4H, aromatic protons). M^+ at *m/e* 240; major peaks at *m/e* 209, 195, 181, 168, 154, 140, 127, 100, 87, 76.

2-*Dioxanyl-benzothiazole* was obtained from benzothiazole by procedure *a* as fine colourless needles. mp 75–76° (light petroleum). (Found: C, 59·82; H, 5·10; N, 6·40. $C_{11}H_{11}NO_2S$ requires: C, 59·71; H, 5·01; N, 6·33%). NMR ($CDCl_3$): 3·4–4·4 (m, 6H, $-C\underline{H}_2-O-$); doublet of doublets center at 5·0 ppm (1H, Ar–$C\underline{H}$(–O–)–); 7·2–8·0 (m, 4H, aromatic protons). M^+ at *m/e* 221; major peaks at *m/e* 193, 163, 135, 108, 69.

2-*Dioxanyl-pyrazine* was obtained from pyrazine by procedure *a* and *b* as colorless needles, mp 63–64° (light petroleum). (Found: C, 57·72; H, 6·20; N, 16·68. $C_8H_{10}N_2O_2$ requires: C, 57·82; H, 6·07; N, 16·86%). NMR ($CDCl_3$): 3·4–4·4 (m, 6H, $-C\underline{H}_2O-$); doublet of doublets center at 4·9 ppm (1H, Ar–$C\underline{H}$(–O–)–); 8·5 (s, 2H, H-5 and H-6); 8·8 (s, 1H, H-3). M^+ at *m/e* 166; major peaks at *m/e* 135, 121, 107, 94, 80.

The 2,5-*di-dioxanyl-pyrazine* (III) was also isolated as a white powder, mp 187–188° (ligroine). (Found: C, 57·09; H, 6·59; N, 10·91. $C_{12}H_{16}N_2O_4$ requires: C, 57·13; H, 6·39; N, 11·10%). NMR ($CDCl_3$): 3·4–4·4 (m, 12H, –$C\underline{H}_2$(–O–)–); doublet of doublets center at 4·85 ppm (2H, Ar–$C\underline{H}$(–O–)–); 8·7 (s, 2H, aromatic protons) (See Fig 1b). M^+ at *m/e* 252; major peaks at *m/e* 193, 132, 106, 80.

A third product, isolated in low yield, mp > 270°, was slightly soluble in common organic solvents. The NMR spectrum pattern was similar to that of the 2-dioxanyl-pyrazine, but only a singlet at 7·9 ppm was present for aromatic protons. The analysis and mass spectrum (M^+ at *m/e* 330) suggested structure (V).

1-*Dioxanyl-isoquinoline* was obtained from isoquinoline by procedure *c* as colourless needles, mp 101 (light petroleum); NMR ($CDCl_3$): 3·8–4·3 (m, 6H, $-C\underline{H}_2-O-$); doublet of doublets center at 5·5 ppm (1H, Ar–$C\underline{H}$(–O–)–); 7·5–7·9 (m, 4H, aromatic protons); 8·1–8·35 (m, 2H, H-3 and H-4). M^+ at *m/e* 215; major peaks at *m/e* 185, 156, 129, 102, 77.

2-*Dioxanyl-quinoxaline* was obtained from quinoxaline by procedure *a* or *b*, mp 65° (reported:[11] 64–65°). Spectral data are identical to those reported.[11] Some 2,3-*di-dioxanyl-quinoxaline* was also isolated. White product, mp 120° (ligroine). (Found: C, 63·65; H, 6·20; N, 9·15. $C_{16}H_{18}N_2O_4$ requires: C, 63·56; H, 6·00; N, 9·27%). NMR ($CDCl_3$): 3·8–4·3 (m, 12H, $-C\underline{H}_2-O-$); 5·2–5·5 (m, 2H, Ar–CH(–O–)–), 7·6–8·3 (m, 4H, aromatic protons). M^+ at *m/e* 302; major peaks at *m/e* 216, 157, 130, 102.

2-(*Tetrahydrofuran-2-yl*)-*quinoxaline* was obtained from quinoxaline by procedure *a* as a pale yellow liquid. The spectral characteristics are identical to those reported.[11]

2-(*Dioxolan-4-yl*)-*quinoxaline* (I) was obtained from quinoxaline by procedure *a* as colourless needles, m.p. 48° (light petroleum). The GLC shows the title compound to be the only reaction product. (Found: C, 65·50; H, 5·05; N, 14·06. $C_{11}H_{10}N_2O_2$ requires: C, 65·34; H, 4·98; N, 13·85%). NMR ($CDCl_3$): 4·1–4·7 (m, 2H, C–$C\underline{H}_2$–O–); 5·2–5·5 (m, 3H, O–$C\underline{H}_2$–O– + Ar–$C\underline{H}$(–O–)–); 9·1 (s, 1H, H-3); 7·7–8·3 (m, 4H, aromatic protons). (Fig 1c). M^+ at *m/e* 202; major peaks at *m/e* 172, 157, 144, 129, 114, 102, 89, 76.

Procedure *c*. Two products having similar retention times were present (2:1). The most abundant was proved (GLC) to be the previous compound (I). We were unable to separate the two products by column chromatography. The mixture was then hydrolyzed with boiling 1:1 HCl, an ethanolic soln of PhNH–NH_2 added, and the precipitated yellow phenylhydrazone, mp 170–171°, was proved to be identical with the one of quinoxaline-2-carboxyaldehyde.

2-(1-*Ethoxyethyl*)-*quinoxaline* was obtained by procedure *a* as a pale yellow liquid, with spectral characteristics identical to those reported.[11]

Alcohols as a source of α-hydroxyalkyl radicals

4-*Hydroxymethyl*-2-*methyl-quinoline*

(a) *From* MeOH *and ammonium peroxydisulphate.* A soln of 2-methyl-quinoline (7·2 g, 0·05 mole) and $(NH_4)_2S_2O_8$ (22·8 g, 0·1 mole) in MeOH (75 ml), H_2O (35 ml) and conc H_2SO_4 (2·7 ml) was refluxed for

24 hr. The excess MeOH was distilled off and the mixture poured on crushed ice, made alkaline with 10% NaOH and extracted with $CHCl_3$. After the evaporation of $CHCl_3$ the crude residue was purified by column chromatography giving a product that was crystallized from ligroine, mp 147° (reported[12] 148°); NMR ($CDCl_3$): 2·57 (s, 3H, CH_3); 5·1 (s, 2H, CH_2); 7·08 (s, 1H, H-3) and 7·4–8·10 ppm (m, 4H, aromatic protons). M^+ at *m/e* 173: major peaks at *m/e* 158, 144, 130 and 115.

(b) *From* MeOH, *ammonium peroxydisulphate and sodium sulphite.* A soln of $(NH_4)_2S_2O_8$ (10 g, 0·044 mole) in H_2O (150 ml) and a soln of $Na_2SO_3 \cdot 7H_2O$ (11 g, 0·044 mole) in H_2O (30 ml) were dropped simultaneously and separately to a stirred soln of 2-CH_3-quinoline (1·43 g, 0·01 mole) in MeOH (30 ml) and conc H_2SO_4 (1·2 ml), with external cooling (temp 0–20°). The mixture was stirred for 30 min at room temp, then refluxed for 30 min. The excess MeOH was distilled off and the residue worked up as in the previous experiment.

(c) *From* MeOH *and sodium perborate.* A soln of 2-methyl-quinoline (7·2 g, 0·05 mole) and $NaBO_3 \cdot 4H_2O$ (15·4 g, 0·1 mole) in MeOH (80 ml), H_2O (80 ml) and conc H_2SO_4 (5·5 ml) was refluxed for 24 hr. At this moment only 25% perborate was decomposed. The reaction mixture was treated as in (A).

(d) *From* MeOH, *sodium perborate and* Fe^{++}. A soln of $NaBO_3 \cdot 4H_2O$ (7·7 g, 0·05 mole) in 10% H_2SO_4 (10 ml) was dropped slowly (15 min) into a stirred soln of 2-CH_3-quinoline (3·6 g, 0·05 mole) and $FeSO_4 \cdot 7H_2O$ (1·4 g, 0·005 mole) in MeOH (50 ml), H_2O (10 ml) and conc H_2SO_4 (1·35 ml), without external cooling and in a N_2 atmosphere. Temp arose from 20° to 60°. The mixture was worked up as in (A).

(e) *From* MeOH, H_2O_2 *and* Cr^{++}. A soln of $CrCl_3 \cdot 6H_2O$ (9 g, 0·034 mole) and Zn pellets (6 g) in 25% H_2SO_4 (v/v) and a second soln of 34% H_2O_2 (4 ml, 0·04 mole) in H_2O (20 ml) were simultaneously and separately dropped into a stirred and refrigerated soln of 2-CH_3-quinoline (4·8 g, 0·03 mole) in MeOH (70 ml), H_2O (10 ml) and conc H_2SO_4 (2 ml) in a N_2 atmosphere. Temp 20–30°. After further stirring (30 min) the reaction mixture was worked up as in (A).

(f) *From* MeOH *and bis(4-t-butylcyclohexyl)peroxydicarbonate.** To a stirred and boiling soln of 2-CH_3-quinoline (3·6 g, 0·025 mole) in MeOH (50 ml) and conc H_2SO_4 (1·35 ml), the solid peroxydicarbonate (10 g, 0·026 mole) was slowly added (30 min). Then H_2O (20 ml) was added and the mixture refluxed for 2·5 hr. The excess MeOH was distilled off, the residue poured on ice, made alkaline with 10% NaOH and extracted with $CHCl_3$. The organic layer was washed with 10% H_2SO_4 and aqueous layer was again made alkaline and extracted with $CHCl_3$. After evaporation the residue was chromatographed and the product crystallized as in (A).

2-Methyl-4-(1-hydroxyethyl)-quinoline

(g) *From* EtOH *and peroxydicarbonate.* The reaction was carried out using procedure (F); obviously EtOH was used in the place of MeOH. By column chromatography two products were isolated: the first was proved to be the expected hydroxyalkylation compound, bp 150–160°/1 mm, of which the spectral characteristics were the same as those of an authentic sample.[13] The second product was the *2-methyl-4-acetyl-quinoline*, (undepressed mp with an authentic sample[13]).

(h) *From* EtOH, *t-butyl-hydroperoxide and* Fe^{++}. A soln of $FeSO_4 \cdot 7H_2O$ (7·2 g, 0·025 mole) in H_2O (15 ml) was dropped in 10 min in a stirred and refrigerated (20°) soln of 2-CH_3-quinoline (3·6 g, 0·025 mole) and t-butylhydroperoxide (2·8 g, 0·025 mole) in EtOH (50 ml), H_2O (10 ml) and conc H_2SO_4 (1·35 ml), the mixture was worked as in (a). The yields (Table 2) were detected by GLC from the pure products as external standards. (Fractovap G.U. Carlo Erba, flame ionization detector; 2 m × 4 mm column packed with 2% XE 60 on sylanized Gaschrom P; temp 158°; carrier: N_2, 30 ml/min).

2- and 4-Hydroxymethyl quinoline

(i) *From* MeOH *and ammonium peroxydisulphate.* A soln of quinoline (6·5 g, 0·05 mole) and $(NH_4)_2S_2O_8$ (22·8 g, 0·1 mole) in MeOH (75 ml), H_2O (35 ml) and conc H_2SO_4 (2·7 ml) was refluxed for 24 hr. The mixture was worked as in (A) and the residue was distilled collecting 3·2 g of an oil boiling in the range 130–170°/2 mm. The GLC analysis, [see (H)] shows the presence of two products (1 : 1) which were separated by preparative GLC (Varian Aerograph 90 P; steel column (2m) packed with 20% XE 60 on sylanized Chromosorb W at 170°; carrier: He at 40 ml/min). First product: mp 64° (reported for 2-CH_2-OH-quinoline: 66–67[13]); second product: mp 95–96° (reported for 4-CH_2-OH-quinoline 97–98°[14]). Also spectral data are in agreement with proposed structures. The mixture of the isomers upon storage in the air, dissolved in chf left a residue that was washed with acetone and crystallized from aqueous pyridine has mp 216–217°

* Perkadox 26, from Noury—Italia

(dec). Spectroscopic techniques suggest the structure: 1,2-*di*-(2-*quinolyl-ethylene-glicol* (VI) (reported[14] mp 212–214° (dec)).

(j) *From* MeOH, *t-butyl-hydroperoxide and* Fe^{++}. A soln of $FeSO_4 \cdot 7H_2O$ (27·8 g, 0·1 mole) in H_2O (100 ml) was slowly (20 min) dropped in a well stirred and refrigerated (10–20°) soln of quinoline (39g, 0·3 mole), t-butyl-hydroperoxide (11·2 g, 0·1 mole) in MeOH (250 ml) and conc H_2SO_4 (22 ml). Then the excess MeOH was evaporated, the residue poured on ice and neutralized with 10% NaOH and extracted with $CHCl_3$. In the organic layer the presence of the two carbinols was detected by GLC. Total yields: see Table 2.

(k) *From* MeOH, H_2O_2 *and* Cr^{++}. The procedure was the same reported in (E), except for the fact that twofold mole of H_2O_2 and Cr^{++} were used with respect to the quinoline. The total yield of the two isomers was detected by GLC (Table 2).

2- *and* 4-(1-*Hydroxyethyl*)-*quinoline*

(l) *From* EtOH, *t-butyl-hydroperoxide and* Fe^{++}. The reaction was carried out as in (J) using a ratio quinoline/radical source 1:2. The mixture of the two isomers was obtained by distillation of the $CHCl_3$ extract, bp 150–160°/3 mm. GLC and NMR confirmed the structures assigned to the two products present in the mixture in a ratio of 1:1.

2-*Hydroxymethyl*-4-*methyl-quinoline*

(m) *From* MeOH *and ammonium peroxydisulphate.* A soln of 4-CH_3-quinoline (14·3 g, 0·1 mole) and $(NH_4)_2S_2O_8$ (22·8 g, 0·1 mole) in H_2O (50 ml), MeOH (100 ml) and conc H_2SO_4 (5·4 ml) was refluxed on a water bath for 24 hr. Working as in (A) a crude product (14·8 g) was obtained that by crystallization from ligroine gave 7·4 g (43%) of a white powder, m.p. 85° (reported[15] for the title compound: 74–75°). (Found: C, 76·40; H, 6·51; N, 7·91. Calc for $C_{11}H_{11}NO$: C, 76·20; H, 6·40; N, 8·09%). NMR ($CDCl_3$): 2·60 (s, 3H, 4-Me); 4·91 (s, 2H, CH_2); 7·06 (s, 1H, H-3); 7·4–8·1 (m, 4H, aromatic protons). M^+ at *m/e* 173, major peaks at *m/e* 144, 128, 115.

2- *and* 4-*Hydroxymethyl-pyridine*

(n) *From* MeOH *and ammonium peroxydisulphate.* This reaction was carried out as in (a) with a ratio pyridine/peroxydisulphate 5:1. The $CHCl_3$ extract was evaporated and the residue distilled. The fraction boiling at 95–105°/1 mm[16] was collected and proved (GLC) to be a mixture of the 2- and 4-hydroxymethyl derivatives, 80% and 20% respectively. This ratio was confirmed by NMR analysis of the mixture on the basis of the peak area of the signals due to the respective methylene groups. NMR ($CDCl_3$): 4·67 (s, CH_2 of the 4-isomer); 4·75 (s, CH_2 of 2-isomer); 7·0–8·0 (H-3 and H-4); 8·3–8·5 (H-2 and H-6. M^+ at *m/e* 109; peaks at *m/e* 92 and 80.

1,2-*Di*-(1-*isoquinolyl*)-*ethylene glicol*

(o) *From* MeOH *and peroxydisulphate.* The reaction was carried out as in (a). By column chromatography of the residue from $CHCl_3$ extract, a product was obtained, mp 182° (EtOH/H_2O). The structure of this product was not completely studied. NMR and mass spectra suggest a dimeric structure similar to that suggested for the dimer formed in the hydroxymethylation of quinoline (I) NMR (DMSO-*d6*): 5·95 (s, 2H,2-CH—OH groups); 7·5–8·5 (m, 12H, aromatic protons). M^+ is lacking; peaks at 171, 157 (M/2), 142, 129.

Procedure for the competitive reactions between 4-*X quinolines and dioxanyl radical*

A 250 ml 4-necked flask, cooled in ice bath, was fitted with an efficient stirrer, two dropping funnels and a thermometer. The flask was charged with 0·01 mole of each of the two 4-X-quinolines dissolved in H_2O (30 ml) and conc H_2SO_4 (6 ml). The p-dioxane /0·2 mole) was added and the stirrer was started. When temp reached 10° t-butyl-hydroperoxide (0·005 mole) and a soln of $FeSO_4 \cdot 7H_2O$ (0·005 mole) in H_2O (15 ml) and conc H_2SO_4 (1 ml) were simultaneously and separately dropped (temp was maintained at 10 ± 1°). After the end of the addition the reaction mixture was basified (pH 10) with 10% NaOH and exaustively extracted with ether. The ether extracted was evaporated to a small volume (50 ml) and the ratio of the dioxanyl derivatives was determined by GLC (procedure *a*), using the pure products otherwise isolated for determining the relative detector response. Results are summarized in Table 3.

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