

44. *Mechanism of Substitution at a Saturated Carbon Atom. Part XXVI. The Rôle of Steric Hindrance. (Section A) Introductory Remarks, and a Kinetic Study of the Reactions of Methyl, Ethyl, n-Propyl, isoButyl, and neoPentyl Bromides with Sodium Ethoxide in Dry Ethyl Alcohol.*

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These papers are concerned with the elucidation of the remarkable inactivity of the *neopentyl* halides in certain substitution reactions (Whitmore, *et al.*). Our general procedure is to relate reactivity to mechanism and its determining factors, structure and experimental conditions, through a study of the rates of reaction of *neopentyl* and other alkyl halides with various reagents under kinetically controlled conditions. In this paper we give the results of an examination of the bimolecular reaction (mechanism S_N2 —see p. 158) of the halides, named in the title, with sodium ethoxide in dry ethyl alcohol. The rate sequence is found to be $\text{Me} > \text{Et} > n\text{-Pr} > \text{isoBu} \gg \text{neopentyl}$, the relative rates ($\text{Et} = 1$) at 55° being: Me 18, Et 1, *n*-Pr 0.28, *iso*Bu 0.030, and *neopentyl* 4.2×10^{-6} . The rate relationships for the first four members are fairly normal for the bimolecular mechanism, for which the rate is decreased by electron accession to the reaction centre, but the *neopentyl* structure has obviously introduced an effect which is far larger than that to be expected on the basis of the electron release of its third methyl group. Evidence is adduced that this effect is of steric origin, but detailed discussion is deferred to the last of this group of papers (Part XXXII, this vol., p. 173).

Introduction to a Group of Papers.

THIS is the first of a small group of connected papers. It will be convenient to give here a very brief description of the nature of the problem undertaken, the method of attack adopted, and the main results obtained.

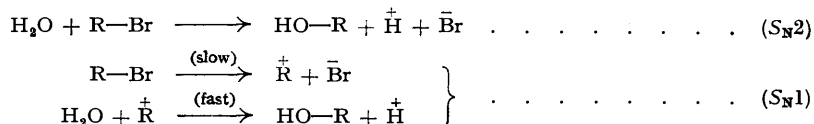
It was shown by Whitmore and his co-workers that the *neopentyl* halides are extraordinarily inactive towards many reagents. Thus, except for the forming of a Gignard reagent and for a reaction with sodium, *neopentyl* chloride did not, under the usual conditions, undergo any of the common reactions of the alkyl halides (Whitmore and Fleming, *J. Amer. Chem. Soc.*, 1933, **55**, 4161; Whitmore, Popkin, Bernstein, and Wilkins, *ibid.*, 1941, **63**, 124). *neopentyl* iodide was, as might be expected, rather more reactive; nevertheless, under conditions which were completely effective for reaction in the case of the *n*-butyl halides, it showed little or no tendency to react with sodium ethoxide, potassium hydroxide or potassium cyanide, though it reacted fairly readily with aqueous silver nitrate. Moreover, when the iodide was caused to react with concentrated alcoholic potash at 180° it gave but a poor yield of ethyl *neopentyl* ether, the major product consisting of *neopentane* (Whitmore, Wittle, and Popkin, *ibid.*, 1939, **61**, 1586). *neopentyl* alcohol also exhibits unusual stability with respect to the action of thionyl chloride and the halides of hydrogen and phosphorus (Whitmore and Rothrock, *ibid.*, 1932, **54**, 3431). In this group of papers we record experimental data and theoretical discussions which contribute towards the elucidation of the properties of these interesting compounds.

In the absence of a certain knowledge of the mechanism of the reactions involved, evidence concerning the reactivity of organic compounds loses much of its significance. In previous papers in this series an attempt has been made, with the aid of kinetic data, to relate reactivity to mechanism. We have applied this method to some of the reactions of *neopentyl* bromide. A satisfactory treatment of the problem involves a study of structural influences by means of a comparison with the corresponding reactions of certain other bromides*;

* Of the halides, the bromides were considered to be the most suitable as a basis for comparison because they are more reactive and less volatile than the chlorides and more free from side reactions than the iodides.

in particular, we have examined the effect of successive methyl substitution as illustrated in the series, CH_3Br , $\text{CH}_3\text{-CH}_2\text{Br}$, $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{Br}$, $(\text{CH}_3)_2\text{CH-CH}_2\text{Br}$, $(\text{CH}_3)_3\text{C-CH}_2\text{Br}$, thereby placing in a certain quantitative perspective some of the peculiarities of *neopentyl* compounds, to which Whitmore had drawn attention in qualitative terms.

The experimental work now described is concerned with the nucleophilic substitutions (S_N) of the halides indicated (cf. Hughes and Ingold, J., 1935, 244 and later papers). For reactions of this type, two distinct mechanisms are recognised, namely a one-stage, bimolecular mechanism (S_N2), involving a direct attack by the nucleophilic substituting agent, and a two-stage, unimolecular mechanism (S_N1), kinetically dependent on the ionisation of the alkyl halide, e.g.,



While the main investigation refers to the behaviour of the halides in reactions which proceed by these or similar mechanisms, the results obtained enable certain conclusions to be reached with respect to the general chemistry of *neopentyl* compounds.

Rate coefficients have been determined for the reactions of certain of the halides (always including *neopentyl* bromide) with the following reagents: (1) sodium ethoxide in dry ethyl alcohol, (2) sodium iodide in acetone, (3) aqueous ethyl alcohol, (4) silver nitrate in aqueous ethyl alcohol,* (5) aqueous formic acid. On the basis of the results obtained, we shall show, *inter alia*, that *neopentyl* bromide is singularly inert towards the bimolecular mechanism, but is moderately reactive under conditions favourable to the unimolecular mechanism. This circumstance makes it possible, under appropriate conditions, to observe the ionisation process in the case of *neopentyl* bromide—an observation which is difficult to achieve with other primary halides. We shall adduce evidence for the view that the cause of the inactivity of the *neopentyl* halides in bimolecular substitution is mainly of a steric character,† and that abnormal behaviour with regard to the ease of elimination of the halogen in these compounds is confined to reactions of the bimolecular type.

The Bimolecular Reaction with Sodium Ethoxide in Dry Ethyl Alcohol.

In this paper we deal with the reactions of the alkyl halides already named with sodium ethoxide in dry ethyl alcohol. All these substitutions are of the second order: they are evidently of the bimolecular type. Some of the necessary data relating to the first four members of the series were already available; the remainder, and all the data for *neopentyl* bromide, were determined in the present work. The rate constants recorded in Table I refer solely to the substitution, a correction having been applied to the total rate constant to allow for the concurrent elimination, leading to olefin, which occurs in some cases. With *neopentyl* bromide we found no evidence for the formation of *neopentane* or the other products which Whitmore and his co-workers (*loc. cit.*) obtained from *neopentyl* iodide and concentrated alcoholic potassium hydroxide at 180° . From the bromide, under the experimental conditions employed in our rate measurements (cf. experimental section), we obtained only ethyl *neopentyl* ether. This may be regarded as auxiliary evidence of the bimolecular nature of this reaction, for in a later paper (this vol., p. 166) we shall show that the unimolecular reaction of the same halide with aqueous ethyl alcohol gives rise to products involving a rearrangement of the carbon structure.

The most striking feature of this comparison is the large decrease in reactivity associated with the *neopentyl* halide. The rate relationships for the first four members are fairly normal for the bimolecular mechanism, for which the rate is decreased by electron-accession to the reaction centre, but the *neopentyl* structure has obviously introduced an effect which is far larger than that to be expected on the basis of the capacity for electron-release of its methyl groups.

In seeking an explanation for this influence we have considered the theory which postulates an electromeric polarisation due to β -hydrogen atoms, $\text{H}-\overset{\curvearrowright}{\text{C}}-\overset{\curvearrowleft}{\text{C}}-\text{Br}$: this would facilitate the separation of the halogen, and decrease in importance as the β -hydrogen atoms are replaced. Such an effect has been shown to be very important in certain cases (Baker and Nathan, J., 1935, 1844; Hughes, Ingold, Masterman, and MacNulty, J., 1940, 899; Hughes, Ingold, and Taher, *ibid.*, p. 949; Baker, *Trans. Faraday Soc.*, 1941, 37, 632; Hughes and Ingold, *ibid.*, p. 657; Baker and Hemming, J., 1942, 191); and, since there are no β -hydrogen atoms available in the *neopentyl* structure, an explanation on this basis is, superficially, of the right form. A detailed consideration shows, however, that it is inadequate in the present instance. First, the electromeric factor

* Reactions of alkyl halides with silver salts in hydroxylic solvents follow modified forms of the general mechanisms (cf. this vol., p. 169).

† This conclusion, and the results on which it was based, were reported in a preliminary form for the Faraday Society's discussion on "Mechanism and Chemical Kinetics of Organic Reactions in Liquid Systems" in September 1941 (cf. *Trans. Faraday Soc.*, 1941, 37, 603). In a paper submitted to the American Chemical Society at about the same time, and published soon afterwards (*J. Amer. Chem. Soc.*, 1942, 64, 543), Bartlett and Rosen concluded that the "*neopentyl* effect" referred to reactions of the S_N2 type and was of a steric nature. Evans and Polanyi (*Nature*, 1942, 149, 608, 665) adopted a similar explanation, and concluded that the steric factor is largely responsible for the comparative inactivity, in bimolecular replacement reactions, of the *tert.*-butyl halides.

TABLE I.

Absolute and Relative Rates for the Bimolecular Substitution Reactions of Primary Bromides with Sodium Ethoxide in Dry Ethyl Alcohol.

[Bromide] $\sim 0.05M$, [NaOEt] $\sim 0.08M$; k_2 = second-order constant in $\text{sec.}^{-1} \text{g.-mol.}^{-1} \text{l.}$

Bromide	Methyl.	Ethyl.	<i>n</i> -Propyl.	<i>iso</i> Butyl.	<i>neo</i> Pentyl.
$10^3 k_2^{55^\circ}$	34.4 ⁽¹⁾	1.95 ⁽²⁾	0.547 ⁽³⁾	0.058 ⁽³⁾	8.26×10^{-6} (4)
Relative rates at 55°	17.6	1	0.28	0.030	4.2×10^{-6}
$10^3 k_2^{95^\circ}$	965 ⁽¹⁾	64.7 ⁽⁵⁾	—	2.62	6.49×10^{-4}
Relative rates at 95°	15	1	—	0.041	1.0×10^{-5}

⁽¹⁾ Calculated from experiments at lower temperatures.

⁽²⁾ Hughes, Ingold, Masterman, and MacNulty, *J.*, 1940, 899.

⁽³⁾ Experiments by M. L. Dhar and S. Masterman. Their work, which was mainly a study of elimination reactions, will be published in detail later (cf. Hughes and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 657).

⁽⁴⁾ Calculated from experiments at higher temperatures.

⁽⁵⁾ Calculated from the results at 55°, assuming an activation energy of 21 kg.-cals. Grant and Hinshelwood (*J.*, 1933, 258) obtained this value for the activation energy of the reaction of ethyl bromide with potassium hydroxide in ethyl alcohol. There is strong evidence that the reaction with alcoholic potash is substantially the same as that with alcoholic sodium ethoxide. Thus, the former reagent, acting on alkyl halides, gives mainly ethers (reaction with OEt) and not alcohols (reaction with OH) (Hughes, Ingold, Masterman, and MacNulty, *loc. cit.*).

should produce a steadier logarithmic decrease in rate from ethyl to *neopentyl*, and could not interpret the much enlarged gap in the rate sequence between *isobutyl* and *neopentyl*. Secondly, the loss of β -hydrogen is just as complete in methyl as in *neopentyl*; yet the methyl halides are highly reactive in bimolecular substitutions, whilst the ethyl halides, in spite of the presence of three β -hydrogen atoms, have a considerably reduced rate of reaction in such substitutions; the effect is even more pronounced in *isopropyl* and *tert.*-butyl halides, although the number of β -hydrogen atoms is still greater (many previous papers of this series). Thirdly, since structural influences which facilitate the separation of halogen as an anion always have a much more pronounced effect on the rates of reactions, proceeding by the unimolecular mechanism than on rates by the bimolecular mechanism, the electromeric effect of the β -hydrogen atoms should operate more strongly in the former mechanism than in the latter. But we show in Part XXXI (this vol., p. 171) that the reactivity of *neopentyl* bromide towards an ionisation mechanism is normal. Finally, Bartlett and Rosen have shown (see footnote, p. 158) that this marked effect of the *tert.*-butyl group attached to the α -carbon atom in *neopentyl* bromide is not primarily due to the operation of any influence of a polar character, since the effect (which they observed in the bimolecular halogen-exchange reaction, $\text{RBr} + \text{KI} \rightarrow \text{RI} + \text{KBr}$) is not capable of transmission through an unsaturated linkage ($-\text{C}\equiv\text{C}-$) interposed between the *tert.*-butyl group and the reaction centre. It is therefore concluded that, in addition to the inductive effect of methyl substituents, there is a superposed effect of a non-polar character, which may in principle enter in all stages of methyl substitution, but which amongst the structures studied, assumed outstanding importance only in the case of the *neopentyl* structure. This effect is concluded to be of steric origin. It is illustrated further in the next paper by reference to the halogen exchange reaction. A theoretical discussion of the effect is contained in Part XXXII (this vol., p. 173).

Arrhenius Parameters.—It is of interest to analyse some of the large differences of rate observed in the present work in terms of the parameters of the Arrhenius equation, $k = Ae^{-E/RT}$. The results of this analysis are given in Table II, where A is in $\text{sec.}^{-1} \text{g.-mol.}^{-1} \text{l.}$ and E is in kg.-cals.

TABLE II.

Arrhenius Parameters for the Bimolecular Substitution Reactions of Primary Alkyl Bromides with Sodium Ethoxide in Dry Ethyl Alcohol.

Bromide	Methyl.	Ethyl.*	<i>iso</i> Butyl.	<i>neo</i> Pentyl.
A	7.2×10^{11}	2.1×10^{11}	9.5×10^{10}	2.3×10^9
E	20.0	21.0	22.8	26.2

* These values relate to the reaction of ethyl bromide with alcoholic potassium hydroxide (Grant and Hinshelwood, *loc. cit.*) and may be considered to be closely comparable to the other figures in the table [cf. Note 5 to Table I].

We do not claim great accuracy for these values, which are obtained from rate measurements at two temperatures only, but they suffice to show that the rate differences (Table I) are due to changes in both A and E .

EXPERIMENTAL.

Exploratory Experiments on the Formation of Halides from neoPentyl Alcohol.—*neoPentyl* alcohol was prepared from formaldehyde and *tert.*-butylmagnesium chloride (Samec, *Annalen*, 1907, **351**, 255; Whitmore and Badertscher, *J. Amer. Chem. Soc.*, 1933, **55**, 1559) or by reduction of ethyl trimethylacetate (Richard, *Ann. Chim. Phys.*, 1910, **21**, 323; *Org. Synth.*, **8**, 104), the latter method being, in our opinion, the more satisfactory. It was fractionated through an all-glass (Pyrex) column (length of packed section = 100 cm.; diam. = 2.2 cm.; efficiency equivalent to 15 theoretical plates) of the total-condensation, adjustable take-off type (Whitmore and Lux, *J. Amer. Chem. Soc.*, 1932, **54**, 3448), which was packed with glass helices (cf. Wilson, Parker, and Laughlin, *J. Amer. Chem. Soc.*, 1933, **55**, 2795; Roper, Wright, Ruhoff, and Smith, *ibid.*, 1935, **57**, 954; Young and Jasaitis, *ibid.*, 1936, **58**, 377), and enclosed in a silvered vacuum jacket fitted with an outer, electrically heated air jacket, which was well insulated and designed to give a small temperature gradient between the bottom and the top.* Interaction of the alcohol (b. p. 113°, m. p. 50°) with thionyl chloride,

* Columns of this type were used throughout the work described in this group of papers.

phosphorus pentachloride, hydrogen chloride or hydrogen bromide failed to yield the *neopentyl* halides (cf. Whitmore and Rothrock, *loc. cit.*), which were therefore prepared from *neopentane* (see below).

Kinetic Measurements.—*neoPentyl* bromide, obtained from *neopentane* via *neopentyl* chloride (Whitmore and co-workers, *J. Amer. Chem. Soc.*, 1939, **61**, 1585), was fractionated through a 15-plate column; b. p. 105°/760 mm. *isoButyl* bromide was obtained from a commercial sample by the usual procedure of removing any *tert.*-butyl bromide which may be present (by hydrolysis with water), and subjecting the unhydrolysed material to careful fractionation; the sample used for the measurements had b. p. 90.5—90.7°/740 mm. Methyl bromide was distilled from phosphorus pentoxide immediately before use. Commercial absolute alcohol was dried by the method of Smith (*J.*, 1927, 1288) as modified by Manske (*J. Amer. Chem. Soc.*, 1931, **53**, 1106), and fractionated.

The thermostats were steady to within 0.02°. In all the experiments described in this paper, the method of sealed bulbs was used. A known amount of the halide was dissolved in the solvent containing the desired quantity of sodium ethoxide, and the solution was made up to 100 ml., usually at 0°. Portions of 5 ml. were enclosed in sealed tubes, which were immersed in the thermostat for known times, and broken under 200 ml. of water. The aqueous solution was then acidified with dilute sulphuric acid and its halide-ion content determined electrometrically. As previously noted (Batesman and Hughes, *J.*, 1940, 947), it was observed that the volume of the reaction tube may be of considerable importance, and the comparative measurements were carried out in small bulbs which were designed to minimise the "free" space above the liquid. It was shown that the addition of crushed glass of the same quality as that of the sealed bulbs had no effect on the rate of reaction. The rate coefficients were calculated from the formula

$$k_2 = [1/(a-b)t] \log_e (b/a)[(a-x)/(b-x)]$$

where *a* and *b* are the initial concentrations of sodium ethoxide and alkyl halide respectively, and *x* is the decrease in concentration after time *t*. The mean values of the rate constants obtained in the comparative experiments are summarised in Table III, and the results of typical experiments are recorded in detail in Table IV. Corrections for thermal expansion between the temperature at which the 5-ml. portions were measured and that of the thermostat have been applied to the mean second-order coefficients of Table III; the results shown in Table IV have not been corrected for expansion.

Since the reaction of *neopentyl* bromide with alkali in *aqueous* ethyl alcohol is of the first order (rate independent of the alkali concentration; cf. this vol., p. 166), the evidence that the reaction with sodium ethoxide in the water-free medium is of the second order should be emphasised. Evidence to this effect is provided by the constancy of the second-order coefficients obtained in experiments in which the two reactants are present in comparable concentrations (Table IV). With a higher initial concentration of sodium ethoxide, the second-order coefficient is but slightly altered, provided this reactant still remains in reasonably low concentration. When the base is present in large excess the coefficient is considerably reduced (Table III); this effect is, however, quite general for bimolecular reactions of this type (cf. previous papers in this series, *e.g.*, Hughes, Ingold, Masterman, and MacNulty, *J.*, 1940, 903). Confirmation for the bimolecular mechanism was obtained through a study of the reaction products (see below).

TABLE III.

Summary of Second-order Rate Constants for the Substitution Reactions of Alkyl Bromides with Sodium Ethoxide in Dry Ethyl Alcohol.

([Bromide] ~0.05M; k_2 in sec.⁻¹ g.-mol.⁻¹ l.)

Bromide.	Initial [NaOEt].	Temp.	$k_2 \times 10^5$.	Bromide.	Initial [NaOEt].	Temp.	$k_2 \times 10^5$.
Methyl	0.077N	20.0°	88.2	<i>neoPentyl</i>	0.077N	95.15°	0.0649
"	0.077N	39.95	786	"	0.935N	95.15	0.0476
<i>isoButyl</i>	0.077N	95.15	262	"	0.077N	125.15	0.963

TABLE IV.

Illustrating Determination of Second-order Rate Constants.

(k_2 in sec.⁻¹ g.-mol.⁻¹ l.)

1. Methyl Bromide at 20.0°. [NaOEt] and [CH₃Br] expressed in ml. of 0.01005N-AgNO₃ per 5 c.c. of solution.

<i>t</i> (mins.)	0	45	60	75	90	105	120	135	180
[CH ₃ Br]	23.35	19.76	18.77	17.81	16.95	16.20	15.47	14.81	12.87
[NaOEt]	37.92	34.33	33.34	32.38	31.52	30.77	30.04	29.38	27.44
$k_2 \times 10^4$	—	8.57	8.52	8.60	8.58	8.50	8.49	8.45	8.62

2. *neoPentyl* Bromide at 125.15°. [NaOEt] and [Bromide] expressed in ml. of 0.01N-AgNO₃ per 5 c.c. of solution.

<i>t</i> (hrs.)	0	24	48	72.5	120	144	168	192.5	218
[Bromide]	23.66	22.42	21.27	20.24	18.44	17.57	16.87	16.02	15.39
[NaOEt]	37.79	36.55	35.40	34.37	32.57	31.70	31.00	30.15	29.52
$k_2 \times 10^6$	—	8.48	8.48	8.35	8.26	8.35	8.21	8.39	8.27

<i>t</i> (hrs.)	240	288	312	354.8	402.8	456	488
[Bromide]	14.64	13.54	12.88	12.25	11.40	10.31	9.82
[NaOEt]	28.77	27.67	27.01	26.38	25.53	24.44	23.95
$k_2 \times 10^6$	8.49	8.41	8.59	8.28	8.25	8.50	8.50

3. *isoButyl* Bromide at 95.15°. [NaOEt] and [Bromide] expressed in ml. of 0.01N-AgNO₃ per 5 c.c. of solution. The second-order rate constants, k_2 , refer to the total reaction (substitution + olefin elimination; cf. below).

<i>t</i> (mins.)	0	2.5	5	7.5	10	13	17	20	30
[Bromide]	25.24	23.74	22.31	20.96	19.88	18.50	16.94	16.11	13.73
[NaOEt]	38.10	36.60	35.17	33.82	32.74	31.36	29.80	28.97	26.59
$k_2 \times 10^3$	—	5.56	5.65	5.79	5.64	5.78	5.84	5.69	5.40
<i>t</i> (mins.)	40	50	60	70	90	120			
[Bromide]	11.40	9.69	8.49	7.51	5.93	4.19			
[NaOEt]	24.26	22.55	21.35	20.37	18.79	17.05			
$k_2 \times 10^3$	5.53	5.63	5.52	5.45	5.35	5.37			

Olefin Estimations.—In the case of *isobutyl bromide*, a bimolecular elimination reaction, leading to formation of olefin, accompanies the bimolecular substitution reaction, and it was necessary to determine the extent of the elimination process in order to decompose the total second-order rate coefficients into their separate components. At certain stages of reaction, or after its conclusion, a number of bulbs were simultaneously removed from the thermostat; some of these were used in the estimation of the extent of the total reaction as indicated in the preceding section, and the remainder for olefin analysis by the extraction method described by Hughes, Ingold, Masterman, and MacNulty (J., 1940, 899). At 95.15°, the mean of several determinations indicated that olefin elimination accounted for 58.2% of the total reaction; the remaining 41.8% is due to the substitution reaction, and this figure was used to calculate the rate constant recorded in Table III.

Reaction Products from neoPentyl Bromide.—*neoPentyl bromide* (0.7 g.), and sodium ethoxide (0.935N) in dry ethyl alcohol (5 ml.) were heated in a sealed tube at 125° for 760 hours. The tube was then cooled and opened, its contents were diluted with water (15 ml.), and the mixture was distilled from a small Claisen flask. The first twelve drops of the distillate were mixed with a concentrated solution of calcium chloride (2 ml.) and the upper layer (ca. 0.5 ml.) was removed with the aid of a micro-pipette. The second twelve drops, treated similarly, yielded only about 0.1 ml. of a top layer, and a third fraction remained homogeneous. The combined upper layers were distilled from fused barium oxide and twice from potassium; m. p. (Emich's method) 91.5°/760 mm., n_D^{20} 1.3805 (Found: C, 72.5; H, 13.8. Calc. for $C_5H_{11}OEt$: C, 72.4; H, 13.8%). [Ethyl *neopentyl ether* has b. p. 90.5°/740 mm. and n_D^{20} 1.3808 (Whitmore, Wittle, and Popkin, *J. Amer. Chem. Soc.*, 1939, **61**, 1586), and ethyl *tert.-amyl ether* has b. p. 101°/760 mm. and n_D^{20} 1.3912 (Evans and Edlund, *Ind. Eng. Chem.*, 1936, **28**, 1186.)

The product obtained from the above experiment is evidently ethyl *neopentyl ether*; no other compound could be isolated. In experiments especially designed to detect *neopentane* or other volatile compounds (cf. p. 158), it was shown that the maximum yield of gaseous product was under 3%.

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