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Abstract

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INVESTIGATION OF THE MECHANISM OF ALKYLATION OF ALCOHOLS BY N-TRIMETHYL-α-PHENETHYLAMMONIUM IODIDE

The aim of our work was to investigate the question of the mechanism of alkylation by an ammonium salt containing a substituted benzyl (α-phenethyl) radical.

It is known that ammonium compounds alkylate alcohols with the formation of ethers. In particular, N-benzyldimethylphenylammonium chloride reacts with alcohols at a temperature of 140–180°, forming benzyl ethers of alcohols ([1]):

$$\mathrm{PhCH_2\overset{\oplus}{N}Me_2Ph + C_5H_{11}OH \longrightarrow PhCH_2OC_5H_{11} + \overset{\oplus}{H}NMe_2Ph}$$

Ammonium salts containing a substituted benzyl radical also enter into the alkylation reaction ([2,3]).

A number of authors have established that alkylation by ammonium compounds is a heterolytic substitution reaction ([1,3,5,6]):

$$\mathrm{R}\left\{\overset{\oplus}{\mathrm{N}}-\right. + \mathrm{Y}:\longrightarrow \mathrm{RY} + :\mathrm{N}-$$

However, up to the present time there have not been sufficient data for deciding the question of precisely how transfer of the radical from the ammonium nitrogen to the molecule of the substance being alkylated (for example, an alcohol) occurs.

Alkylation reactions by ammonium compounds, belonging to substitution reactions of the S_N type, may proceed by two pathways:

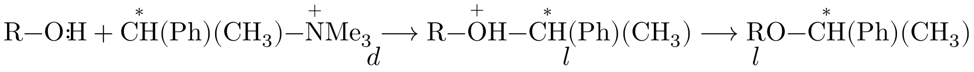
1. Formation of the new bond occurs simultaneously with rupture of the old one. Such reactions are called synchronous. A characteristic example of synchronous processes is provided by reactions proceeding through an activated complex.

2. Formation of the new bond is preceded by complete rupture of the old bond. In this case free carbon ions are formed. Such reactions are called asynchronous.

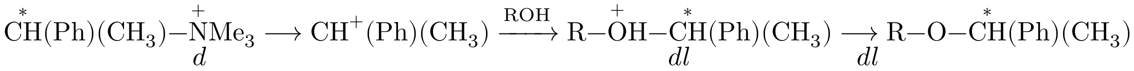
The use of optically active substances makes it possible to distinguish synchronous processes from asynchronous ones. Synchronous reactions at an asymmetric center are accompanied by inversion (or retention) of configuration, whereas asynchronous reactions (proceeding through the intermediate formation of free carbon ions) are accompanied by complete racemization, which is a consequence of the planar structure of carbonium ions.

We studied the alkylation of methyl, ethyl, and *n*-butyl alcohols by the optically active salt *d*-N-trimethyl-*α*-phenethylammonium.

In this case, if the reaction proceeds by a synchronous mechanism, then, on the basis of what was said above, preservation of optical activity by the reaction products should occur; but if the reaction proceeds by an asynchronous mechanism, then the reaction product should be devoid of optical activity:

(A)


$$\text{(A)}\quad R{-}O{:}H + \overset{*}{C}H(Ph)(CH_3){-}\overset{+}{N}\underset{d}{Me_3} \longrightarrow R{-}\overset{+}{O}H{-}\underset{l}{\overset{*}{C}H}(Ph)(CH_3) \longrightarrow \underset{l}{R}O{-}\overset{*}{C}H(Ph)(CH_3)$$

(B)


$$\text{(B)}\quad \overset{*}{C}H(Ph)(CH_3){-}\underset{d}{\overset{+}{N}}Me_3 \longrightarrow CH^{+}(Ph)(CH_3) \xrightarrow{\text{ROH}} R{-}\overset{+}{O}H{-}\underset{dl}{\overset{*}{C}H}(Ph)(CH_3) \underset{dl}{\longrightarrow} R{-}O{-}\overset{*}{C}H(Ph)(CH_3)$$

The alkylation reaction was studied in the temperature range 135–155° (at temperatures below 135° the alkylation of alcohols by iodide of N-trimethyl-*α*-phenethylammonium proceeds at too low a rate). The solvent was the alcohol being alkylated, taken in excess. The *α*-phenethyl alkyl ethers formed as a result of the reaction were studied polarimetrically.

It was found that in all the cases investigated the ethers obtained possessed no optical activity. However, it remained unclear whether racemization occurs during the alkylation reaction or in the initial ammonium salt as a result of heating with alcohol at high temperature. To clarify this question, we carried out the reaction under such conditions that the iodide of *d*-N-trimethyl-*α*-phenethylammonium did not react completely. The unreacted iodide of N-trimethyl-*α*-phenethylammonium was then isolated from the salt mixture by fractional crystallization. It turned out that the salt isolated from the reaction mixture had almost completely retained its initial optical activity, whereas the *α*-phenethyl methyl ether obtained was entirely devoid of optical activity.

It follows from the data obtained that the alkylation reaction of alcohols with the N-trimethyl-*α*-phenethylammonium salt proceeds through the intermediate formation of the *α*-phenethylcarbonium ion, i.e., by an asynchronous mechanism (scheme (B)).

Experimental part

1. *d*-N-dimethyl-α-phenethylamine. A mixture of 156 g of pure *l*-malic-acid *d*-α-phenethylamine (^{7}), 180 ml of 85% formic acid, and 175 ml of 30% formalin was heated at 95° for 10 hr; then 75 ml of conc. hydrochloric acid was added, after which the formic acid and water were distilled off in vacuo. The residue was dissolved in water, alkalized, and steam-distilled. The distillate was shaken with 20 ml of acetic anhydride, alkalized, and extracted with benzene. The product obtained was fractionated on a column. The yield of *d*-N-dimethyl-α-phenethylamine reached 73.2 g (81% of theory); n_D^{20} 1.5022-1.5024; d_4^{20} 0.9027-0.9030; $[\alpha]_D^{23} = +70.8-71.6°$ (without solvent)*.

It has been reported (^{8}) that *l*-N-dimethyl-α-phenethylamine has $[\alpha]_D^{24} - 65.3°$.

2. **Iodide of *d*-N-trimethyl-α-phenethylammonium** was obtained from *d*-N-dimethyl-α-phenethylamine and methyl iodide by the method known from the literature (^{9}). Recrystallized from a mixture of acetone and ether, it had m.p. 157-157.5°**, $[\alpha]_D^{20} = +12.3°$ (in H_2O, $C = 8.8\%$).

3. **Interaction of iodide of *d*-N-trimethyl-α-phenethylammonium with methyl alcohol.** 0.05 mol of iodide of *d*-N-trimethyl-α-phenethylammonium and 0.2 mol of absolute methyl alcohol were heated in a sealed ampoule at $136 \pm 1°$ for 5 hr.

The contents of the ampoule were treated with 50 ml of absolute, peroxide-free ether. The ammonium salts were rapidly filtered off by suction and washed on the filter with a small amount of ether. The ethereal solution obtained was washed with water, 0.5 *n* sulfuric acid solution, and once more with water, after which was dried with potash. The solvent was distilled off on a column. There was isolated 1.63 g of α-phenethyl methyl ether with b.p. 68.5-69.5° (20 mm), n_D^{20} 1.4951.

Determination of the optical activity showed that the ether obtained is a racemic substance.

From the mixture of ammonium salts insoluble in ether (11.5 g), by recrystallization from acetone-ether, there were obtained 2.21 g of tetramethylammonium iodide and 7.51 g of N-trimethyl-α-phenethylammonium iodide, having m.p. 142.6-143.5°. Determination of the optical activity showed that the salt which had not entered into the reaction possessed a specific rotation differing only slightly from the specific rotation of the initial *d*-N-trimethyl-α-

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* In a similar manner, on methylation of *l*-α-phenethylamine *d*-tartrate, optically pure *l*-N-dimethyl-α-phenethylamine was obtained, $[\alpha]_D^{25} = -71.2°$ (without solvent).

** The *dl*-salt has m.p. 147-148°.

phenethylammonium iodide ($[\alpha]_D^{20} = +11.5°$ instead of $+12.3°$ for the initial salt).

The data presented show that alkylation of methyl alcohol proceeds with the intermediate formation of the α-phenethylcarbonium ion.

The results of experiments on the alkylation of methyl alcohol with N-trimethyl-α-phenethylammonium iodide are given in Table 1.

4. **Reaction of *d*-N-trimethyl-α-phenethylammonium iodide with ethyl alcohol.** 0.1 mole of *d*-N-trimethyl-α-phenethylammonium iodide and 0.42 mole of absolute ethyl alcohol were heated in a sealed ampoule for 11 hr at 135-7°.

Table 1

Configuration of the ammonium ion	Alkylation temperature, °C	Reaction duration, hr	n_D^{20}	b.p., °C (mm)	Configuration of α-phenethyl methyl ether
dl	130	8	1.4950	62-64 (17)	–
dl	155-8	4	1.4948	56-57 (12)	–
d	153-5	4	1.4946	75-78 (32)	*dl*
d	135-7	5	1.4951	68.5-69.5 (20)	*dl*

The reaction mixture was treated with 100 ml of 0.2 N H_2SO_4, filtered, and extracted with methylene chloride. The extract obtained was washed with water and with $NaHCO_3$ solution, and dried with $MgSO_4$. After distilling off the solvent and fractional distillation, 4.3 g of pure ethyl α-phenethyl ether was obtained, b.p. 60.5-61.0° (8 mm). The substance possessed no optical activity ($[\alpha]_D^{20} = 0 \pm 0.2°$).

Found, %: C 79.78; H 9.34
$C_{10}H_{14}O$. Calculated, %: C 79.98; H 9.39

5. **Reaction of *l*-N-trimethyl-α-phenethylammonium iodide with *n*-butyl alcohol.** 0.05 mole of *l*-N-trimethyl-α-phenethylammonium iodide (optical purity 59.8%) and 0.17 mole of dry butyl alcohol were heated in a flask with a reflux condenser under nitrogen for 5.5 hr at 125 ± 3°.

The reaction mixture was treated with 25 ml of H_2O and extracted with benzene.

The benzene solution of the organic substances was washed with water, 2 N H_2SO_4, again with water, 10% soda solution, and dried with K_2CO_3.

There was obtained 1.89 g of butyl α-phenethyl ether with b.p. 90.5–91.0° (8 mm), n_D^{20} 1.4812, d_4^{20} 0.902. The substance proved to be devoid of optical activity, ($[\alpha]_D^{20} = 0.1 \pm 0.2°$).

Found, %: C 81.07; H 10.04
$C_{12}H_{18}O$. Calculated, %: C 80.82; H 10.17

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Note: Figure translations are in progress. See original paper for figures.