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THE BECKMANN REARRANGEMENT OF ALIPHATIC KETOXIMES. A COMPARISON OF THE INFLUENCE OF REAGENTS ON THE COURSE OF THE REARRANGEMENT[1]

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As pointed out previously (1), Hantzsch (2) reports that two amides are obtained from the Beckmann rearrangement of methyl isopropyl ketoxime whereas Sidgwick (3) states that only one is obtained. The principal product from the oxime

$$CH_3C(=NOH)R \qquad I$$

was shown by Hantzsch to be

$$CH_3CONHR \qquad II$$

when R is ethyl, *n*-propyl, isopropyl, or *n*-hexyl. The same is true for $C_2H_5C(CH_3)_2CH_2C(=NOH)CH_3$ and $(CH_3)_3CCH(CH_3)C(=NOH)CH_3$ as was found by Drake *et al.* (4). A similar result is obtained for 2-alkylcyclohexanone oximes which bear a formal resemblance to I (5, 6, 7, 8). To clear up the discrepancy in the literature, to discover whether the conditions of rearrangement are influential in determining the course of the reaction, and to decide whether preferential rearrangement is primarily caused by steric or electronegativity effects of $CH_3(CH_2)_n$- compared to CH_3- or C_2H_5- in aliphatic ketoximes, a quantitative study of this rearrangement has been carried out on a number of compounds with phosphorus pentachloride in ether (Table I) and sulfuric acid (Table II) as reagents.

The yields were about eighty per cent or higher, as previously reported (4). In view of yields less than one hundred per cent it was necessary to establish that all of the amides were recovered for calculation of mole fractions of products. This point was substantiated as described under Experimental.

The first factor investigated was the influence of the nature of R (Table I). It was observed that the mole fraction of *n*-alkyl amine varies from 0.66 to 1.03 with perhaps an alternation of mole fraction with number of carbon atoms in the homologous series of R. On the other hand, as the bond angle within R varied from 0° (*n*-propyl) to 60° (cyclopropyl) to 109° (isopropyl), the mole fraction of RNH_2 increased from 0.66 to 0.88 to 1.03 (or unity). This may indicate a steric hindrance in the neighborhood of $-\overset{|}{C}=NOH$. The inductive effects of the groups, however, are in the same order. A Fisher-Hirschfelder model of methyl isopropyl ketoxime shows a small amount of restricted rotation of isopropyl about $-C(=NOH)-CH_3$ for the syn form of the oxime. Thus the course of the re-

[1] From the M.S. thesis of R. E. Schachat, 1948.

arrangement may be influenced by the ratio of the geometrical isomers of the parent oximes. This is probably also true of 2-alkylcyclohexanone oximes.

That the difference observed in the mole fractions of RNH_2 from methyl *n*-propyl and methyl cyclopropyl ketoximes is real is shown by application of the

$$t = \frac{\overline{X}_1 - \overline{X}_2}{\left(\frac{n_1 + n_2}{n_1 + n_2 - 2}\right)^{1/2} \left(\frac{\Sigma(X_1 - \overline{X}_1)^2 + \Sigma(X_2 - \overline{X}_2)^2}{n_1 n_2}\right)^{1/2}}$$

"t" test (9). The quantity t is derived as for any two sets of data of n_1 and n_2 observations. By referring to a table supplied by Rider (9), t is converted to P (| t |) known as the "level of significance." Generally, if one finds a "level of significance" greater than .05 it cannot be concluded that any difference between the two sets has been shown. As an illustration, if two sets of observations were compared in the above manner and P (| t |) = 0.06, we could say that the level of significance was 6% or that there are about 6 chances in 100 of observing a *greater* difference between the two sets of data, even if both sets consisted of observations made on the same or identical systems. In the above instance of methyl *n*-propyl ketoxime (giving a mole fraction $RNH_2 \cdot HCl$ equal to 0.66 ± 0.07) and methyl cyclopropyl ketoxime (giving a mole fraction $RNH_2 \cdot HCl$ equal to 0.88 ± 0.18) $t = << .01$, therefore we may conclude with reasonable certainty that the two oximes give distinctly different mole fractions of RNH_2.

To see whether or not an electronegativity effect (1, 3) of propyl as compared to ethyl could also be observed, ethyl *n*-propyl ketoxime was rearranged. Again the migration of nitrogen was predominantly toward the longer radical, the more electron-releasing group (10).

Whether methyl isopropyl ketoxime rearranges to give but one amide as stated by Sidgwick, or two amides as claimed by Hantzsch apparently depends upon conditions of the rearrangement. With phosphorus pentachloride in ether or with 85% sulfuric acid and heat only one product was formed. With 93% sulfuric acid nearly equal amounts of the two amides were produced. This reaction took place with much more violence than the reaction with 85% acid. The behavior of oximes with phosphorus pentachloride as catalyst is further shown to be qualitatively different from that with 93% sulfuric acid by comparison of the respective yields from ethyl *n*-propyl ketoxime, Tables I and II. One can propose that at room temperature preponderently one form of the oxime exists for rearrangement but that under the high temperature of comparatively violent reaction in sulfuric acid more nearly equal amounts of both forms of oximes or the corresponding sulfate esters are available for rearrangement. No further explanation for the results can be offered until a study has been made of the composition of the oximes themselves, *i.e.*, syn or anti, as a function of temperature and solvent composition.

Finally, it may be pointed out that steric reasons are not the whole story since the greater than 0.5 mole fraction of *n*-propylamine from ethyl propyl ketoxime is an indication that the electrical fields of ethyl and propyl are different (10).

EXPERIMENTAL

Rearrangements with phosphorus pentachloride in ether. The oximes, prepared from the corresponding ketones in the usual way (7), were rearranged with phosphorus pentachloride in ether as described by Drake *et al.* (4) or in sulfuric acid (8). With the first method, the ether was removed by distillation on a steam-bath and the residue of amides from 0.5–1.0

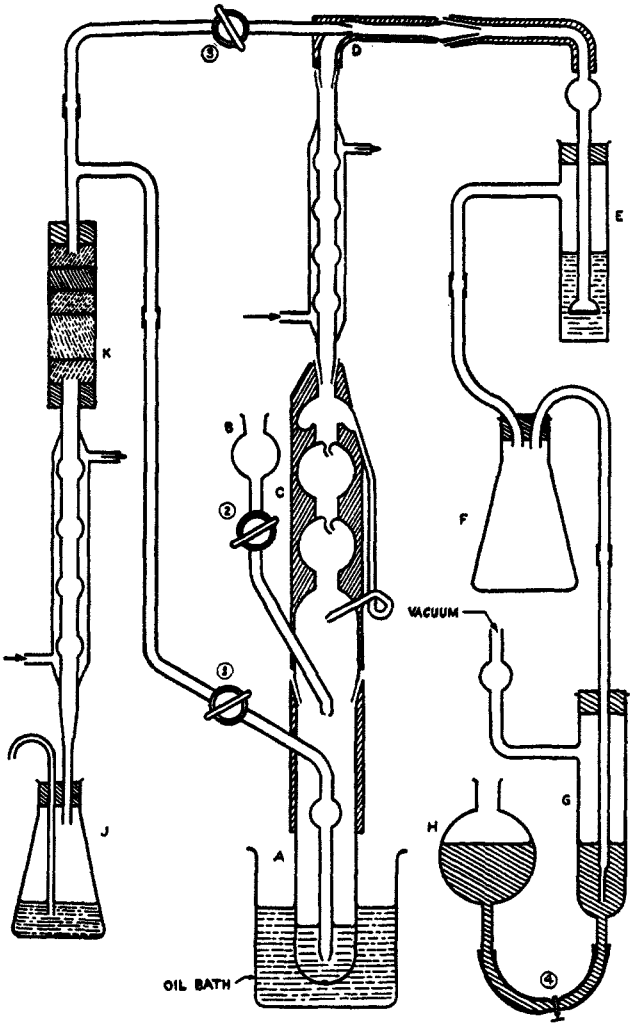

FIGURE 1. AMINE DISTILLATION APPARATUS

g. of oxime was poured onto 5–10 g. of ice in vessel A of the amine distillation apparatus (Fig. 1). This apparatus is an extensive modification of the ammonia entrainment apparatus of Lecoq (11). The transfer was made quantitative with the aid of boiling-water washings. After freezing the mixture of amides and washings, the apparatus was assembled as shown in Figure 1. Stopcocks "1" and "2", and screw clamp "4" were closed; stopcock "3" was left open. "E" contained 50 ml. of 2 *N* hydrochloric acid, "J" contained concentrated sulfuric acid, "G" and "H" contained mercury, "K" contained substances to remove

moisture and basic gases from the incoming air. A vacuum was applied to pressure regulator "G" so that a fine but steady stream of bubbles was drawn through the fritted glass disk on the inlet tube in "E". Incoming air entered the system by bubbling through the sulfuric acid of "J", then passed through absorption tube "K", through stopcock "3", through the dilute hydrochloric acid of "E", through trap and pressure-steadier "F", and finally through pressure regulator "G". With the air being drawn through the system as described above, 10 ml. of 10 *N* potassium hydroxide solution was cautiously added to "A" through funnel "B". The oil-bath was heated to 120–130° and maintained for two hours at this temperature producing gentle reflux. The amides in "A" were completely hydrolyzed by this treatment, causing amines to be released. The volatile amines passed through the reflux condenser, were caught in the air stream at point "D", and were dissolved in the hydrochloric acid at "E". The oil-bath was removed and the mixture allowed to cool for 10–15 min. without interruption of the air stream. Then, the condenser between "C" and "D" was removed and "D" was connected directly to "C". Stopcock "3" was closed, stopcock "1" was immediately opened, and the air flow was increased until it was two or three times its former rate. The oil-bath was replaced in its original position and heated to 190–220°, driving water and all amines into "E" where they were trapped. During this part of the process, vessel "E" was continuously cooled by a jet of cold water. About 5 minutes after dryness was reached in vessel "A", vessel "E" was removed from the system after which the vacuum was released.

The alkaline material in "A" was dissolved in a small quantity of water and extracted with chloroform. The chloroform solution was extracted with 2 *N* hydrochloric acid and the acidic solution was then combined with the distillate in "E". Evaporation from a weighed flask left a residue of amine hydrochlorides which were dried to constant weight. The chloride in the residue was converted to silver chloride according to Kolthoff and Sandell (12). The weight of silver chloride was used to compute the apparent molecular weight of the mixture of amine hydrochlorides as follows:

$$\text{app. mol. wt.} = \frac{143.34\ (\text{wt. of amine hydrochlorides})}{\text{weight silver chloride}}$$

From the apparent molecular weights of the amine hydrochloride mixtures, the absolute amounts of the two amines derived from the rearrangement were computed graphically by means of a molecular weight of amines versus mole fraction plot in the usual way. The results with known quantities of amides show that any carry-over of inorganic alkali into the chloroform was negligible or nil (see below).

Rearrangements with 93% sulfuric acid. About 0.5 g. of oxime was accurately weighed into a 125-ml. Erlenmeyer flask. One milliliter of 93% sulfuric acid was added. To prevent spattering, the flask was covered by a small funnel. The mixture was heated on a hot plate until a reaction had taken place, *i.e.*, about 110°. After cooling, the mixture was washed onto 5–10 g. of ice in receptacle "A" of the entrainment apparatus. Hydrolysis of the amides and distillation of the amines were performed as described above. Rearrangements with 85% sulfuric acid were performed in a similar manner.

Discussion of errors. (a) *Degree of rearrangement.* A sample of methyl *n*-propyl ketoxime was rearranged with phosphorus pentachloride in the usual manner. Instead of hydrolyzing the amides they were extracted with chloroform and weighed. The yield was 83.7% in excellent agreement with the results of Table I for this compound. That is, this method of rearrangement only produced an 84% yield; the fact that 16% of the material fails to rearrange cannot affect conclusions based on the results in Tables I and II. Aliphatic ketoximes apparently do not rearrange as completely with phosphorus pentachlorides in ether as with sulfuric acid (4, 5).

As shown with di-*n*-butyl ketoxime, any decomposition products from the rearrangement of unreacted ketoxime did not affect the molecular weight of the *n*-butylamine produced by more than 2%, Table I.

(b) *Stability of the cyclopropyl compounds.* A sample of methyl cyclopropyl ketoxime was rearranged and the resulting amides were hydrolyzed. The methylamine was allowed to escape while cyclopropylamine was retained and converted to its hydrochloride, m.p. 99° (13). In sulfuric acid rearrangements the cyclopropyl ring was destroyed.

(c) *Losses due to incomplete distillation of amines, incomplete hydrolysis, escape of amines from the hydrochloric acid solution, non-quantitative transfers, volatilization of the amine*

TABLE I

BECKMANN REARRANGEMENT OF KETOXIMES WITH PCl_5

KETOXIME	YIELD OF PRODUCTS, AVERAGE %	MOLE FRACTION[a] $RNH_2 \cdot HCl$[b]	NUMBER OF DETERMINATIONS
Methyl ethyl	81.0	0.73 ± 0.06	4
Methyl *n*-propyl	83.6	0.66 ± 0.07	6
Methyl isopropyl	83.0	1.03 ± 0.00	2
Methyl cyclopropyl	80.1	0.88 ± 0.18	7
Methyl *n*-butyl	73.6	0.79 ± 0.13	7
Methyl *n*-amyl	75.9	0.68 ± 0.23	6
Methyl *n*-hexyl	72.8	0.69 ± 0.03	4
Ethyl *n*-propyl	73.7	0.85 ± 0.18	6
Di-*n*-butyl	40.2	0.98	1

[a] Mole fractions are given as plus or minus 2σ where

$$\sigma = \sqrt{\frac{\Sigma (X - \bar{X})^2}{n}} \sqrt{\frac{n}{n-1}}$$

and n is the number of determinations; $(\bar{X} - \bar{X})$ is the difference between individual values, X, and the mean, $\bar{X}$.

[b] R = longer chain.

TABLE II

BECKMANN REARRANGEMENT OF KETOXIMES WITH 93% H_2SO_4

KETOXIME	YIELD OF PRODUCTS, AVERAGE %	MOLE FRACTION OF $RNH_2 \cdot HCl$	NUMBER OF DETERMINATIONS
Methyl *n*-propyl	87.6	0.79 ± 0.05	3
Methyl isopropyl	87.8	0.57 ± 0.06	5
Ethyl *n*-propyl	92.3	0.58 ± 0.05	3
Methyl isopropyl[a]	85.5	1.01 ± 0.18	2

[a] Rearrangement with 85% sulfuric acid.

hydrochloride while drying, etc. A series of compounds was used to assay the method, Table III. The explanation of the Table is as follows.

A weighed amount of *n*-amylamine hydrochloride was inserted into vessel "A" of the apparatus, an excess of potassium hydroxide solution was added, and 99.4% of the amine was recovered upon distillation and reconversion to the hydrochloride (Exp. 1). Weighed amounts of known amides were hydrolyzed and then distilled. The recovery was about 96% (Exps. 2, 3, 4). Weighed amounts of two different amides were placed in the apparatus, hydrolyzed and distilled. The recovery was about 93% and the experimental percentages of amines agreed closely with the expected (Exps. 5, 6, 7).

SUMMARY

A series of aliphatic ketoximes were rearranged and the mole fractions of the resulting amides were determined.

In all cases the rearrangement favored the formation of amides of the form R^1CONHR where R is longer than R^1. The relative proportion of the favored form increased in the order R = *n*-propyl, cyclopropyl, isopropyl, with phosphorus pentachloride in ether as catalyst.

TABLE III

STANDARDIZATION OF THE EQUIPMENT

EXP. NO.	COMPOUND USED	RESULTS
1	*n*-Amylamine hydrochloride	M.W. (theo.): 123.6; M.W. (exp.): 124.6. Recovery: 99.4%
2	N-Ethyl acetamide	M.W. (theo.): 81.5; M.W. (exp.): 83.8. Recovery: 96.0%
3	N-Ethyl acetamide	M.W. (theo.): 81.5; M.W. (exp.): 83.0. Recovery: 96.6%
4	N-*n*-Amyl acetamide	M.W. (theo.): 123.6; M.W. (exp.): 120.1. Recovery: 95.7%
5	N-Ethyl acetamide and N-*n*-Amyl acetamide	% Ethylamine (theo.): 52.0% % Ethylamine (exp.): 49.6% Total Recovery: 92.8%
6	N-Ethyl acetamide and N-*n*-Amyl acetamide	% Ethylamine (theo.): 72.2% % Ethylamine (exp.): 72.6% Total Recovery: 93.7%
7	N-Ethyl acetamide and N-*n*-Amyl acetamide	% Ethylamine (theo.): 58.9% % Ethylamine (exp.): 56.8% Total Recovery: 91.6%

The mole fractions of amides obtained from aliphatic ketoximes was different with phosphorus pentachloride than with 93% sulfuric acid.

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