CCCXIX.—*The Isomerism of the Oximes. Part XXVII. The Mechanism of Methylation of the Aldoximes.*

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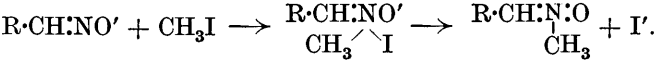
In a previous paper (Brady, Dunn, and Goldstein, this vol., p. 2398), it was shown that, when the sodium salts of the α-aldoximes are methylated in alcoholic or aqueous solution, a mixture of *O*- and *N*-ethers was formed, the *O*-ether preponderating. Goldschmidt (*Z. Elektrochem.*, 1908, **14**, 581) studied the velocity of methylation by methyl iodide of the sodium salts of some α-aldoximes in alcoholic solution. He concluded that the α-*O*-ethers were produced by a bimolecular reaction between the ion of the oxime and methyl iodide, $R\cdot CH{:}NO'+CH_3I\rightarrow(R\cdot CH{:}NO')(CH_3I)\rightarrow R\cdot CH{:}N\cdot OCH_3+I'$. Further, he found that the methylation of the β-aldoxime sodium salts, in which the *N*-ether is the main product, also proceeded as a bimolecular reaction for which a similar mechanism was assumed:



$$R\cdot CH{:}NO' + CH_3I \longrightarrow \begin{array}{c}R\cdot CH{:}NO'\\ CH_3\diagup\diagdown I\end{array} \longrightarrow \begin{array}{c}R\cdot CH{:}N{:}O\\ |\\ CH_3\end{array} + I'.$$

Both these assumptions are open to question, since Goldschmidt overlooked the production of a considerable amount of *N*-ether in the methylation of α-aldoximes. Our work on this subject (Brady, Dunn, and Goldstein, *loc. cit.*) suggested that there was a relation between the amount of *O*-ether formed and the degree of dissociation of the sodium salt of the oxime, and a quantitative study of the methylation of a number of α-aldoximes has now been made.

The method consisted in dissolving the oxime in aqueous sodium hydroxide and methylating at room temperature with methyl sulphate. The products were removed by extraction with chloroform, and the unchanged oxime was determined in the aqueous portion, so that the amount of oxime actually methylated was known. In the estimation of the products of methylation, advantage was taken of the non-reactivity of the *O*-ethers; the chloroform was removed and the mixed methyl ethers were boiled with concentrated hydrochloric acid for a short time, whereby the *N*-ether was completely hydrolysed to aldehyde and β-methylhydroxylamine hydrochloride, leaving the *O*-ether unchanged. The aldehyde and *O*-ether were removed by extraction and the β-methylhydroxylamine was determined in the aqueous portion by a specially devised iodometric method.

The amounts of *O*- and *N*-methyl ethers formed on methylating several substituted benzaldoximes in 2*N*-solution have been determined and the effects of varying the concentrations of the reactants and of adding a common ion have been investigated, the results being summarised in Tables I and II.

Difficulties in technique make it impossible to claim a high standard of accuracy for the results, but repetitions have given sufficiently concordant values to justify the conclusion that they are approximately correct.

TABLE I.

(Sodium oximate, 2*N*.)

Oxime.	Ratio of *N*- : *O*-ether.	$10^{11} \times K_a$ of oxime.
α-3 : 4-Methylenedioxybenzaldoxime	1 : 1·86	1·4
α-*o*-Methoxybenzaldoxime	1·98	1·3
α-*p*-Methoxybenzaldoxime	2·16	1·2
α-Benzaldoxime	2·43	2·1
α-*m*-Methoxybenzaldoxime	2·60	2·6
α-*o*-Nitrobenzaldoxime	2·84	8·7
α-*m*-Nitrobenzaldoxime	3·62	7·0
α-2 : 4-Dinitrobenzaldoxime	12·0 *	37·0

* Only very approximate, as the amount of *N*-ether obtained was too small to be determined accurately.

TABLE II.

Oxime.	Ratio of *N*- : *O*-ether. 2*N*-Sodium oximate.	0·5*N*-Sodium oximate.	2*N*-Sodium oximate +2*N*-NaOH.	2*N*-Sodium oximate +4*N*-NaCl.
α-Benzaldoxime	1 : 2·43	—	—	1 : 2·00
α-*m*-Nitrobenzaldoxime	3·62	1 : 3·88	—	—
α-*p*-Methoxybenzaldoxime	2·16	2·59	1 : 2·65	1·86
α-3 : 4-Methylenedioxybenzaldoxime	1·86	2·55	2·61	—

Owing to the insolubility of the sodium salt of α-*p*-nitrobenzaldoxime, the methylation could be carried out only in 0·5*N*-solution and the ratio *N*- : *O*-ether was then 1 : 3·88; similar difficulties were experienced with other oximes in the presence of sodium chloride, etc.

The results are in harmony with the view that the *N*-ether is produced by the interaction of methyl sulphate with the undissociated sodium salt of the oxime, and the *O*-ether by an ionic reaction. For example, increasing the ionisation by dilution or by the addition of sodium hydroxide increases the amount of *O*-ether formed, whilst the addition of a common ion, thereby increasing the concentration of the sodium salt, results in more *N*-ether being produced (Table II). In addition, Table I indicates that the proportion of *N*-ether formed varies inversely as the magnitude of the dissociation constant. With *o*-methoxy-, *o*-nitro-, and 3 : 4-methylenedioxy-benzaldoximes, the amount of *N*-ether formed is greater than it should be, and in these cases there is apparently some other influence at work, possibly a steric one; it is noteworthy that ortho-substituted aldoximes are often anomalous in their behaviour.

It has already been shown that the β-aldoximes on methylation yield much more *N*- than *O*-ether (Brady, Dunn, and Goldstein, *loc. cit.*); for example, the ratios of *N*- to *O*-ether obtained from β-*p*-methoxy-, β-3 : 4-methylenedioxy-, and β-*m*-nitro-benzaldoximes were 1 : 0·11, 1 : 0·08, and 1 : 0·61, respectively; a similar explanation will account for this behaviour, since the β-aldoximes are much weaker acids than the corresponding α-compounds (Brady and Goldstein, this vol., p. 1923). The interaction of an α-aldoxime with methyl iodide or methyl sulphate to give exclusively the *N*-ether (Brady, Dunn, and Goldstein, *loc. cit.*) must also be represented as a molecular reaction, the hydriodide or methosulphate being the first product formed, $\mathrm{R{\cdot}CH{:}N{\cdot}OH + MeI \longrightarrow R{\cdot}CH{:}N(OH)MeI}$.

On this view, there are two simultaneous reactions proceeding during the methylation of the sodium salts of the oximes: an ionic one giving the *O*-ether, and a molecular one the *N*-ether. With the high concentrations employed, it must also be assumed that the *O*-ether is produced in part by a molecular reaction by simple metathesis between the sodium salt of the oxime and methyl sulphate, on the analogy of the alkylation of the alcohols. By the application of Wegscheider's test it can be shown that the above reactions are all of the same order: Table III shows that the percentage of *N*-ether formed in the methylations at different stages is independent of the time.

TABLE III.

Oxime.	Wt. taken.	Wt. unacted upon.	% *N*-ether.
α-*m*-Nitrobenzaldoxime	5·00 g.	1·58 g.	20·2
,, ,,	5·00	0·82	20·8
α-*p*-Methoxybenzaldoxime	4·50	1·51	27·2
,, ,,	4·50	0·84	28·5
α-3 : 4-Methylenedioxybenzaldoxime	5·00	1·21	27·2
,, ,, ,,	5·00	0·88	27·5

The first two oximes were methylated in 0·5*N*-solution and the last in 2*N*-solution in the presence of excess of sodium hydroxide.

The amount of *N*-ether produced by methylating the sodium salts of two α-aldoximes with methyl iodide in alcoholic solution has also been determined, and it has been found that the proportion of *N*- to *O*-ether is approximately the same in 0·1*N*-alcoholic solution as in 2*N*-aqueous solution (compare Luxmoore, J., 1896, **69**, 186).

It must be pointed out that our interpretation of our results assumes that in 2*N*-solution there is a considerable amount of undissociated sodium oximate; if, however, the salts are completely dissociated at this concentration in accordance with recent theories of strong electrolytes, another explanation must be sought.

In connexion with this work, mention must be made of the investigations of Claisen (*Z. angew. Chem.*, 1923, **36**, 478; *Annalen*, 1925, **442**, 210) on the *C*-alkylation of phenols. He has shown, for example, that whilst, in dissociating solvents, sodium phenoxide and allyl bromide give more than 90% of allyl phenyl ether, in non-dissociating media as much as 70% of *o*-allylphenol is produced. It appears, therefore, that the views developed in this paper are of wide application; it has already been found that they can be applied to the methylation of the hydroxybenztriazoles (Brady and Day, J., 1923, **123**, 2258, and unpublished work) and we propose to extend it in other directions.

EXPERIMENTAL.

Determination of β-Methylhydroxylamine.—The β-methylhydroxylamine hydrochloride was prepared by the reduction of nitromethane with zinc dust in neutral solution (Beckmann, *Annalen*, 1909, **365**, 204); it is best purified by two or three crystallisations from a mixture of boiling absolute alcohol and ethyl acetate, washing the crystals with dry ether, and drying over potassium hydroxide in a vacuum, being then obtained in colourless, odourless crystals, m. p. 88—89°. The method of purification described in the literature—precipitation of a solution in absolute alcohol with ether—is unsatisfactory.

According to Kirpal (*Ber.*, 1892, **25**, 1715), β-methylhydroxylamine can be determined by weighing the cuprous oxide it precipitates from boiling Fehling's solution according to the equation

$$3CH_3{\cdot}NH{\cdot}OH + 6CuO = 3Cu_2O + CH_3{\cdot}NH_2 + 2NH_3 + 2CO_2 + 2H_2O.$$

We cannot confirm this statement, since, when β-methylhydroxylamine was boiled with Fehling's solution, very variable results were obtained, 1 mol. requiring, *e.g.*, $\frac{7}{8}$, $2\frac{3}{4}$, $3\frac{1}{4}$, and $1\frac{3}{4}$ atoms of oxygen.

An alternative possibility was the reduction of iodine in potassium iodide by β-methylhydroxylamine hydrochloride in the presence of sodium bicarbonate, and after some trouble satisfactory conditions have been devised for obtaining concordant results. A roughly *N*/10- to *N*/20-solution of β-methylhydroxylamine hydrochloride was run into a mixture of 25 c.c. of *N*/30-iodine in potassium iodide, 75 c.c. of water, and 75 c.c. of a saturated solution of sodium bicarbonate. With the burette used (time of flow for 50 c.c. = 35 secs.), about four-fifths of the necessary amount of the β-methylhydroxylamine solution was run in all at once without shaking, and the rest more slowly, the end-point being determined by starch indicator; the temperature of the iodine solution was kept at 10—15°. Under these conditions concordant titration values could be obtained and the reaction appears to be stoicheiometrical, 1 mol. of β-methylhydroxylamine requiring 2 atoms of iodine. The method was checked against β-methylhydroxylamine hydrochloride and against two *N*-ethers. For example, 0·5083 g. of β-methylhydroxylamine hydrochloride was dissolved in water and diluted to 250 c.c.; successive portions of 25 c.c. of 0·03256*N*-iodine, diluted as before, required 16·9, 17·0, and 16·8 c.c. (mean 16·9) of the β-methylhydroxylamine solution. If the reaction is stoicheiometrical, this indicates 98·9% of β-methylhydroxylamine hydrochloride in the sample used. Again, 0·9725 g. of *N*-methyl-*m*-nitrobenzaldoxime was boiled under reflux with 10 c.c. of concentrated hydrochloric acid and 5 c.c. of water for 20 minutes, and the *m*-nitrobenzaldehyde formed by hydrolysis was removed by extraction with chloroform. The aqueous residue was neutralised with the calculated amount of potassium bicarbonate, made up to 250 c.c., and the β-methylhydroxylamine determined as above. Successive amounts of 25 c.c. of the iodine solution required 19·3, 19·4, 19·2, 19·5, and 19·2 c.c. of the above solution (mean 19·3), giving 97·5% of *N*-ether in the sample taken. Finally, 0·9368 g. of *N*-methyl-3 : 4-methylenedioxybenzaldoxime was treated as above, 25 c.c. of the iodine solution requiring 19·6, 19·8, and 19·8 c.c. (mean 19·7 c.c.) of the β-methylhydroxylamine solution, indicating 98·6% of *N*-ether in the sample taken.

We have not yet been able to identify with certainty the products of the oxidation of β-methylhydroxylamine under these conditions, but it seems probable that formaldoxime is the primary product ($CH_3{\cdot}NH{\cdot}OH + O = CH_2{:}N{\cdot}OH + H_2O$). In any case, Kirpal's equation cannot apply, since no methylamine could be detected in the reaction mixture by Valton's method (J., 1925, **127**, 40), and boiling with alkali for 2 hours gave only 10% of the nitrogen as ammonia. The reaction is being further investigated.

The Quantitative Methylation of the Aldoximes.—(*a*) *In* 2N-*solution.* The general method was as follows : The oxime (0·03 g.-mol.) was dissolved in 18 c.c. of 2*N*-sodium hydroxide (0·036 g.-mol.) and 3 c.c. of methyl sulphate (0·032 g.-mol.), previously washed and dried over anhydrous sodium sulphate, were added. The mixture was cooled under the tap and shaken frequently for 10—20 minutes. The combined ethers formed were extracted with several portions of chloroform, and the extracted mixed ethers, after evaporation of the solvent, were boiled with 10 c.c. of concentrated hydrochloric acid and 5 c.c. of water under reflux for ½—1½ hours; aldehyde and *O*-ether were removed by extraction with chloroform and the β-methylhydroxylamine in the aqueous solution was determined as above. Meanwhile, the unchanged oxime left in the aqueous portion of the methylation mixture after removal of the ethers was determined by adding a saturated solution of ammonium chloride and extracting with chloroform. The solvent was removed on the water-bath, and the oxime dried in the steam-oven and weighed. The results are accurate to within about 5%. The direct determination of the *O*-ether proved to be impracticable owing to its volatility.

The total yield of ethers (*T*) was calculated from the amount of oxime methylated, as determined from the difference between the quantities employed and recovered (*W*, *w*), and the yield of *N*-ether (*N*) from the β-methylhydroxylamine, the ratio of *N*- to *O*-ether being given by *N* : (*T*—*N*). The results are given in Table IV.

Table IV.

Oxime.	*W.*	*w.*	*N.*	*T.*	$100N/T$.	$N:(T-N)$.
α-Benzaldoxime (1)	3·60 g.	0·30 g.	1·09 g.	3·68 g.	29·6	1 : 2·36
„ „ (2)	3·60	0·16	1·10	3·84	28·6	2·49
α-*o*-Nitrobenzaldoxime (1) ...	5·00	0·38	1·30	5·01	25·9	2·85
„ „ (2) ...	5·00	0·42	1·30	4·97	26·2	2·82
α-*m*-Nitro- „ (1) ...	5·00	0·34	1·11	5·05	22·0	3·55
„ „ (2) ...	5·00	0·33	1·08	5·06	21·3	3·69
α-2 : 4-Dinitro- „ ...	3·61*	2·50	0·09	1·18	7·6	12·1
α-*o*-Methoxy- „ ...	3·00†	0·16	1·04	3·10	33·5	1·98
α-*m*-Methoxy- „ ...	4·50	0·38	1·25	4·50	27·8	2·60
α-*p*-Methoxy- „ (1) ...	4·50	0·04	1·52	4·87	31·2	2·20
„ „ (2) ...	4·50	0·11	1·54	4·80	32·1	2·12
α-3 : 4-Methylenedioxybenzaldoxime (1)	5·00	0·35	1·77	5·05	35·0	1·85
α-3 : 4-Methylenedioxybenzaldoxime (2)	5·00	0·33	1·76	5·07	34·7	1·88

* With 2 : 4-dinitrobenzaldoxime, 10·25 c.c. of 2*N*-sodium hydroxide and 1·7 c.c. of methyl sulphate were used; owing to the very low concentration of β-methylhydroxylamine in the solution for titration, the value for *N* is inaccurate, but the experiment goes to show that a low proportion of *N*-ether is formed on methylation.

† Using 12 c.c. of 2*N*-sodium hydroxide and 2 c.c. of methyl sulphate.

(*b*) *In* 0·5N-*solution.* The oximes (0·03 g.-mol) dissolved in 72 c.c. of 0·5*N*-sodium hydroxide (0·036 g.-mol.) were methylated with 3 c.c. of methyl sulphate under similar conditions and the product was treated as before; the results are given in Table V.

Table V.

Oxime.	*W.*	*w.*	*N.*	*T.*	$100N/T$.	$N:(T-N)$.
α-*m*-Nitrobenzaldoxime (1) ...	5·00 g.	0·82 g.	0·94 g.	4·53 g.	20·8	1 : 3·82
„ „ (2) ...	5·00	1·58	0·75	3·71	20·2	3·95
α-*p*-Nitro- „ (1) ...	5·00	1·75	0·74	3·52	21·0	3·76
„ „ (2) ...	5·00	1·42	0·78	3·89	20·1	3·99
α-*p*-Methoxy- „ (1) ...	4·50	1·51	0·89	3·27	27·2	2·67
„ „ (2) ...	4·50	0·84	1·14	4·00	28·5	2·51
α-3 : 4-Methylenedioxybenzaldoxime (1)	5·00	0·77	1·27	4·59	27·7	2·61
α-3 : 4-Methylenedioxybenzaldoxime (2)	5·00	0·84	1·29	4·51	28·6	2·50

(*c*) *In excess of sodium hydroxide.* The amounts of material taken were: oxime, 0·030 g.-mol.; 4*N*-sodium hydroxide, 18 c.c. (0·072 g.-mol.); and methyl sulphate, 3 c.c. (0·032 g.-mol.).

(*d*) *In the presence of sodium chloride.* The amounts of material taken were: oxime, 0·030 g.-mol.; 2*N*-sodium hydroxide, 18 c.c. (0·036 g.-mol); sodium chloride, 4·27 g. (0·073 g.-mol.); and methyl sulphate, 3 c.c. (0·032 g.-mol.).

The results of both (*c*) and (*d*) are given in Table VI.

TABLE VI.

Oxime.	W.	w.	N.	T.	$100N/T$.	$N:(T-N)$.
	(*c*) In excess of sodium hydroxide.					
α-*p*-Methoxybenzaldoxime (1)	4·50 g.	0·73 g.	1·12 g.	4·12 g.	27·2	1 : 2·68
,, ,, (2)	4·50	0·68	1·15	4·17	27·6	2·63
α-3 : 4-Methylenedioxybenzaldoxime (1)	5·0	1·21	1·12	4·11	27·3	2·67
α-3 : 4-Methylenedioxybenzaldoxime (2)	5·0	0·88	1·25	4·47	28·0	2·58
	(*d*) In presence of sodium chloride.					
α-Benzaldoxime (1)	3·60	0·18	1·30	3·82	34·0	1·94
,, (2)	3·60	0·17	1·25	3·83	32·6	2·06
α-*p*-Methoxybenzaldoxime (1)	4·50	0·04	1·73	4·87	35·7	1·82
,, ,, (2)	4·50	0·06	1·68	4·85	34·6	1·89

The means of the values given in the foregoing tables were used in the theoretical part.

Methylations in the presence of excess of sodium hydroxide or of sodium chloride could not be carried out with a larger number of oximes owing to the precipitation of the sodium salt.

(*e*) *In alcoholic solution.* (1) α-*m*-Nitrobenzaldoxime. Sodium (0·74 g.; 0·032 g.-mol.) was dissolved in 301 c.c. of absolute alcohol and pure α-*m*-nitrobenzaldoxime (5·00 g.; 0·030 g.-mol.) added, giving an *N*/10-solution; methylation was effected by pure redistilled methyl iodide (4·54 g.; 0·032 g.-mol.); after being kept for 18 days the solution reacted neutral. Concentrated hydrochloric acid (10 c.c.) was added and the solution distilled in steam for 3 hours to remove alcohol, aldehyde, and *O*-ether, and the β-methylhydroxylamine hydrochloride remaining in the flask was determined. A preliminary experiment had shown that α-*m*-nitrobenzaldoxime was completely methylated by the action of a slight excess of methyl iodide and sodium in alcohol over a period of 3 days. Oxime taken = 5·00 g.; *N*-ether found = 0·92 g.; total amount of ethers formed = 5·42 g.; percentage of *N*-ether = 17·0; ratio of *N*- to *O*-ether = 1 : 4·89.

(2) α-3 : 4-Methylenedioxybenzaldoxime. The following quantities were used: oxime, 4·87 g. (0·029 g.-mol.); methyl iodide, 4·34 g. (0·030 g.-mol.); sodium, 0·71 g. (0·031 g.-mol.); and absolute alcohol, 295 c.c.; after 17 days, the product was treated as before: *N*-ether found = 1·90 g.; total ethers formed = 5·28 g.; percentage of *N*-ether = 36·0; ratio of *N*- to *O*-ether = 1 : 1·78.

Summary.

(1) The relative amounts of *O*- and *N*-ethers formed under various experimental conditions in the methylation of the aldoximes have been determined.

(2) The results are in agreement with the assumption that the *O*-ether is produced essentially by an ionic reaction between the oxime ion and the alkyl compound, and that the *N*-ether is produced by addition of the alkyl compound to the undissociated sodium oximate.

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