CCCXVIII.—*The Isomerism of the Oximes. Part XXVI. The Methyl Ethers of the Aldoximes.*

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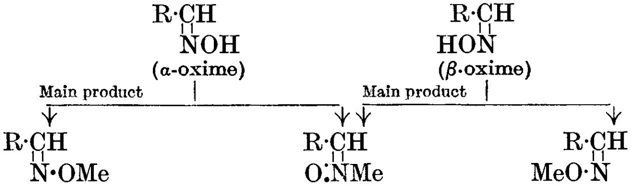
Despite the importance attaching to the alkyl derivatives in connexion with the theories of oxime isomerism, little experimental work has been done on the methylation of the aldoximes since that of the early investigators of this subject (Gabriel and Meyer, *Ber.*, 1881, **14**, 2337; Gabriel, *Ber.*, 1882, **15**, 3067; Petraczek, *Ber.*, 1883, **16**, 826; Goldschmidt and co-workers, *Ber.*, 1890, **23**, 2163; 1891, **24**, 2548, 2808; 1893, **26**, 2103).

Werner ("Lehrbuch der Stereochemie," 1904, p. 277) states clearly that on methylation the α-aldoximes give mainly the *O*-ether with some *N*-ether, and the β-aldoximes mainly the same *N*-ether as that obtained from the α-aldoxime and some of the isomeric *O*-ether. Adopting the new configuration (Brady and Bishop, J., 1925, **127**, 1357), this statement may be represented diagrammatically thus :



Werner also says that different oximes give different proportions of the two ethers; he gives, however, no references to the experimental work on which these views were founded, but our own experience soon confirmed their correctness (Brady, J., 1914, **105**, 2108, 2110). Although Goldschmidt and Zanoli (*Ber.*, 1892, **25**, 2587) observed that α-furfuraldoxime gave both the *O*- and the *N*-ether on methylation, and Beckmann (*Ber.*, 1889, **22**, 1535) was aware that two ethers were formed in the alkylation of α-oximes, yet Goldschmidt (*Z. Elektrochem.*, 1908, **14**, 581), in his work on the velocity of methylation of the sodium salts of α-aldoximes, seems to have considered either that no *N*-ether was formed or that it was formed in such small quantities as not to influence his results. The solubility of the *N*-ethers in water and their sparing solubility in ether are the probable reasons for their formation having been overlooked; for example, the distribution coefficient of *N*-methyl-3 : 4-methylenedioxybenzaldoxime between ether and water is 1 : 7. They can, however, be extracted from aqueous solutions by chloroform.

The stereochemical hypothesis demands two isomeric *N*-ethers from unsymmetrical oximes and, although two have been obtained from certain ketoximes (Semper and Lichtenstadt, *Ber.*, 1918, **51**, 928; Plowman and Whiteley, J., 1924, **125**, 587; Brady and Mehta, *ibid.*, p. 2297), yet it is remarkable that there is no example of a pair of isomeric *N*-ethers of any aldoxime (compare Goldschmidt and Zanoli, *loc. cit.*; Scheiber, *Annalen*, 1909, **356**, 215).

This communication forms the first part of a detailed study of the methyl ethers of the aromatic aldoximes; the main problems that have been considered are : (1) a search for the second *N*-ether, (2) the best method of preparing the β-*O*-ethers, and (3) a qualitative (and roughly quantitative) investigation of the products of methylation of the aldoximes under various conditions, as a preliminary to more accurate quantitative measurements.

No evidence has been obtained of the existence of a second

N-ether, although twelve of these compounds have been prepared by the methylation of the α- and β-oximes with methyl iodide and methyl sulphate under differing conditions, and by the action of β-methylhydroxylamine on the aldehydes. This last method of preparation seems to have been little employed in cases where the *N*-ethers can be obtained from the β-oxime (compare, however, Beckmann, *Annalen*, 1909, **365**, 208). The hydrochlorides of the *N*-ethers have been prepared and the ethers regenerated from them without any indication of the formation of an isomeride.

The action of methyl sulphate on solutions of α- and β-aldoximes in sodium hydroxide has been investigated. This reagent was used by Ponzio and Charrier (*Gazzetta*, 1907, **37**, i, 508), who isolated only the *O*-ether from α-benzaldoxime and α-*p*-methoxybenzaldoxime; indeed, they recommend this reagent as giving the *O*- and not the *N*-ether in the case of acetaldoxime (compare Dunstan and Goulding, J., 1901, **79**, 635). Ponzio and Charrier state that they obtained crystalline chloroplatinates from their *O*-ethers, a result we have been unable to confirm; moreover, it seems very unlikely that such compounds would be formed, since all attempts to obtain hydrochlorides of *O*-ethers have been unsuccessful, these compounds being, apparently, devoid of basic properties; on the other hand, the *N*-ethers form chloroplatinates and it seems that Ponzio and Charrier's supposed pure *O*-ethers contained some *N*-ether.

Our methylations of the α-aldoximes have been carried out by dissolving 1 equiv. of the oxime in $1\frac{1}{6}$ equivs. of 2*N*-sodium hydroxide, and shaking at room temperature with slightly more than 1 equiv. of methyl sulphate. Under these conditions, considerable quantities of *N*-ether are formed—in some cases as much as 40% of the total yield of ethers. Ponzio and Charrier's method, using 30% sodium hydroxide, would give a smaller proportion of *N*-ether, as will be shown in a subsequent paper.

The large amount of *N*-ether formed eliminates the possible explanation that the so-called α-oximes are equilibrium mixtures of the two isomerides (compare Cameron, *J. Physical Chem.*, 1898, **2**, 409), since, if the β-isomeride was present in so great an amount, it would be impossible to overlook the nitrile which would inevitably be formed on treatment with acetic anhydride and alkali; moreover, the *N*-ether is obtained in fair quantity from oximes which are known only in one form, *e.g.*, from *o*-methoxybenzaldoxime.

A few experiments have been made on the methylation of the α-aldoximes with methyl iodide in methyl alcohol in the presence of sodium methylate, and here again the *N*- in addition to the *O*-ether is formed.

When the α-aldoximes are dissolved or suspended in methyl iodide or methyl sulphate and kept in the dark for some time, in many cases they are converted into the hydriodides or methosulphates of the *N*-methyl ethers, no trace of the *O*-compounds being formed. These salts on decomposition with sodium carbonate give the same *N*-methyl derivative as is obtained by the other methods of preparation. Luxmoore (J., 1896, **69**, 183) thought he had obtained a second *N*-ether from the hydrobromide of *N*-methyl benzaldoxime, but it was ultimately shown to be a hydrate (Scheiber, *loc. cit.*); we have had similar experiences.

The exclusive formation of *N*-ether in non-ionising media, and the proportions of *N*-ether formed by methylation of different oximes in sodium hydroxide solution with methyl sulphate, suggested that the relative amounts of the two ethers formed bore some relation to the dissociation constants of the oximes—the more acidic the oxime the smaller the amount of *N*-ether formed. Further evidence for this view will be brought forward in a subsequent communication.

The β-*O*-methyl ethers have previously been obtained by the action of methyl iodide on the dry silver salts of the β-oximes; this preparation is troublesome, but we have found that good results are obtained by boiling the β-oxime under reflux with methyl iodide, ether, and dry silver oxide. β-O-*Methyl*-m-*nitro*-p-*methoxybenzaldoxime* has been obtained by this method as a crystalline solid, this being the third case where both *O*-methyl ethers of an aldoxime have been definitely characterised.

EXPERIMENTAL.

The Action of β-*Methylhydroxylamine on Aldehydes.*

Various methods of preparation have been employed, partly with the object of ascertaining whether variation of procedure would give the second *N*-ether, and partly owing to the different properties of the aldehydes and *N*-ethers.

(1) 3 : 4-*Methylenedioxybenzaldehyde.*—(*a*) The aldehyde (5 g.), dissolved in the minimum amount of alcohol, was mixed with β-methylhydroxylamine hydrochloride (2·75 g.), also in the minimum of alcohol, and a solution of sodium (0·76 g.) in alcohol added. After being kept over-night, the alcohol was removed on the water-bath and the residue extracted three times with boiling benzene. Most of the solvent was removed on the water-bath and the remainder evaporated at room temperature in a current of air. On crystallising the solid from benzene–light petroleum, there separated colourless plates of N-*methyl*-3 : 4-*methylenedioxybenzaldoxime hydrate*, m. p. 77°, which lost water on keeping for 48 hours over solid sodium hydroxide (Found : N, 7·4; H_2O, 9·4. $C_9H_9O_3N,H_2O$ requires

N, 7·1; H_2O, 9·1%). N-*Methyl*-3 : 4-*methylenedioxybenzaldoxime* crystallises from benzene in colourless plates, m. p. 108° (Found: N, 7·9. $C_9H_9O_3N$ requires N, 7·8%).

(*b*) The following was a quicker method: The aldehyde (16 g.) was just melted under water (50 c.c.) and β-methylhydroxylamine hydrochloride (10 g. in 50 c.c. of water) added, followed by sodium hydroxide (5 g. in 25 c.c. of water). On shaking, the oil dissolved, and after a few minutes the hydrate of *N*-methyl-3 : 4-methylenedioxybenzaldoxime separated and was collected, washed with a very small quantity of water, and air-dried; yield 18 g. of crude product, m. p. 75—76°. From the filtrate and washings a further 2 g. were recovered by extracting twice with chloroform.

(2) *Benzaldehyde.*—The aldehyde (13 g.) was suspended in 2*N*-sodium hydroxide (70 c.c.) and β-methylhydroxylamine hydrochloride (11 g. in 25 c.c. of water) added. After shaking for 5 minutes, the aldehyde had disappeared; the *N*-methylbenzaldoxime remaining in solution was extracted four times with chloroform; after removal of the solvent on the water-bath, the residue solidified on cooling and scratching and was dried for some days over solid sodium hydroxide. On crystallising from benzene and light petroleum pure *N*-methylbenzaldoxime (m. p. 82°) was obtained in almost theoretical yield. The m. p. is given in the literature as 69—72° but this low value is probably due to the presence of hydrate, since we have found that, however prepared, the compound always has the higher m. p. when carefully purified and dried.

(3) p-*Nitrobenzaldehyde.*—(*a*) The aldehyde (9 g.) was dissolved in the minimum amount of hot alcohol and a solution of β-methylhydroxylamine hydrochloride (5 g.) in alcohol added; *N*-methyl-*p*-nitrobenzaldoxime began to crystallise at once. After the mixture had cooled, it was separated, washed with a little alcohol and air-dried, 8 g. of the pure compound (m. p. 208°) being obtained. A small quantity of the same compound, but less pure (m. p. 200—205°), was obtained by diluting the mother-liquors. The feeble basicity of *N*-methyl-*p*-nitrobenzaldoxime—its hydrochloride is very readily hydrolysed, see below—and its sparing solubility enable the aldehyde to react with β-methylhydroxylamine hydrochloride in the absence of alkali.

(*b*) A solution of β-methylhydroxylamine hydrochloride (2 g.) in alcohol was mixed with one of sodium (0·6 g.) in alcohol, the precipitated sodium chloride removed and the filtrate added to *p*-nitrobenzaldehyde (3·5 g.) dissolved in alcohol (60 c.c.) at 35°. The colour changed to green, then orange, and yellow crystals began to separate which were collected after 30 mins. and found to be *N*-methyl-*p*-nitrobenzaldoxime (m. p. 205°). The mother-liquors were diluted and the precipitate (m. p. 160°) subjected to a careful fractional crystallisation, but only the ordinary *N*-ether and some unchanged *p*-nitrobenzaldehyde were recovered.

(4) 6-*Nitro*-3 : 4-*methylenedioxybenzaldehyde.*—Method (3*b*) was employed using 5 g. of aldehyde in 100 c.c. of warm alcohol, 5 g. of β-methylhydroxylamine hydrochloride and 0·7 g. of sodium. N-*Methyl*-6-*nitro*-3 : 4-*methylenedioxybenzaldoxime* crystallises from hot water or from alcohol in deep yellow, dichroic needles, m. p. 210° (decomp.) (Found : N, 12·8. $C_9H_8O_5N_2$ requires N, 12·5%).

(5) 3 : 4-*Dimethoxybenzaldehyde.*—Method (1*a*) was employed, using 4 g. of aldehyde in 20 c.c. of alcohol, 2·5 g. of β-methylhydroxylamine hydrochloride, and 0·7 g. of sodium. On cooling the benzene extract, the *N*-ether crystallised in good yield; after recrystallising from benzene, N-*methyl*-3 : 4-*dimethoxybenzaldoxime* was obtained in faintly pink leaflets, m. p. 127° (Found : N, 7·5. $C_{10}H_{13}O_3N$ requires N, 7·2%).

(6) o-*Methoxybenzaldehyde.*—Method (1*a*) was employed, using 6 g. of aldehyde in 15 c.c. of alcohol, 4 g. of β-methylhydroxylamine hydrochloride, and 1·1 g. of sodium. The benzene extract, on concentrating and scratching, deposited crystals which, after crystallising from benzene–light petroleum, gave N-*methyl*-o-*methoxybenzaldoxime* in felted masses of long, white needles, m. p. 85° (Found : N, 8·7. $C_9H_{11}O_2N$ requires N, 8·5%). When this compound was dissolved in a very small quantity of hot water and the solution cooled in a freezing mixture, a *hydrate* separated, m. p. 27—28°; this loses water very readily and it was found impossible to determine its composition; after pressing on a porous tile, the loss in weight on drying over sodium hydroxide varied between 21 and 40%. The compound, therefore, probably contains more than one mol. of water of crystallisation.

(7) p-*Chlorobenzaldehyde.*—Method (1*a*) was employed, using 5 g. of aldehyde, 5 g. of β-methylhydroxylamine hydrochloride and 0·9 g. of sodium, and extracting with hot chloroform instead of with benzene. After crystallising twice from benzene, N-*methyl*-p-*chlorobenzaldoxime* was obtained in colourless plates, m. p. 128° (Found : N, 8·5. C_8H_8ONCl requires N, 8·3%).

(8) o-*Nitrobenzaldehyde.*—The aldehyde (7 g.) in warm alcohol (25 c.c.) was mixed with β-methylhydroxylamine hydrochloride (4·5 g.) in the minimum amount of water, and a concentrated aqueous solution of potassium acetate (5 g.) added. After 2 hours, excess of water was added and the solution extracted twice with chloroform. The extract on evaporation gave an oil which solidified on seeding; after crystallisation from benzene–light petroleum, 5 g. of *N*-methyl-*o*-nitrobenzaldoxime were obtained;

m. p. 92°. Occasionally this compound crystallised in a mixture of two forms, long needles and plates; after separation by hand, both forms melted at 92°, and a mixture at the same temperature.

(9) m-*Nitrobenzaldehyde*.—(*a*) Method (8) was employed, using 7 g. of aldehyde in 25 c.c. of warm alcohol, 4·5 g. of β-methylhydroxylamine hydrochloride and 5 g. of potassium acetate. The dilution of the mixture with water resulted in the precipitation of *N*-methyl-*m*-nitrobenzaldoxime (m. p. 110—114°) which was collected and then washed with a small quantity of water; the filtrate and washings on extraction with chloroform gave a further quantity of *N*-ether. One crystallisation from benzene–light petroleum gave the pure compound (m. p. 118—119°) in each case. Method (3*b*) was also used, but the same *N*-ether was obtained.

(*b*) The aldehyde (15 g.) and β-methylhydroxylamine hydrochloride (10 g.) in alcohol (100 c.c.) were warmed for 2 hours at 50° (compare Beckmann, *Annalen*, 1909, **365**, 201). On dilution with water, an oil and a solid were obtained which were taken up with ether; on removing the ether at room temperature, an oil and a solid remained; they were filtered at the pump, and the solid was washed with a little ether; a crude *N*-methyl-*m*-nitrobenzaldoxime (m. p. 97°) remained, which after one crystallisation from benzene gave the pure compound. The filtrate and ether washings on evaporation gave an oil from which *m*-nitrobenzaldehyde slowly crystallised. The oily residue was dissolved in ether and saturated with hydrogen chloride; the precipitate, on decomposition with sodium carbonate, gave the ordinary *N*-methyl ether, and the ethereal solution on evaporation yielded *m*-nitrobenzaldehyde. In this case, the reaction was incomplete, but no indication of the formation of a new *N*-ether was obtained.

When *N*-methyl-*m*-nitrobenzaldoxime is crystallised from hot benzene, it separates in long, fine needles; if these are left for some weeks in contact with the mother-liquor, the bulky crystals slowly disappear and are replaced by compact, rhombic crystals; both forms have the same m. p. alone or mixed.

(10) p-*Methoxybenzaldehyde*.—Method (2) was employed, using the same quantities but shaking for 30 minutes. After removing the chloroform, the oil was kept in an evacuated desiccator over solid sodium hydroxide for 24 hours and it then solidified on seeding. Crystallisation from light petroleum gave the pure *N*-ether, m. p. 76°. This compound is particularly troublesome to crystallise and light petroleum is the only solvent which gives satisfactory results, although it dissolves but little; the compound absorbs moisture from the atmosphere to form the monohydrate (m. p. 45°), and this crystallises unchanged from light petroleum; the

water is, however, lost on keeping for some time in a vacuum over solid sodium hydroxide.

(11) *Cinnamaldehyde.*—Method (1*a*) was employed, using 5 g. of aldehyde, 3·5 g. of β-methylhydroxylamine hydrochloride, and 0·95 g. of sodium. After removing most of the alcohol, the mixture was diluted with water, a tarry product filtered off, and the solution extracted twice with chloroform. On removing the solvent, a brown oil was obtained which solidified after 24 hours; it was pressed on a porous tile and crystallised from light petroleum containing a very little benzene; N-*methylcinnamaldoxime* separated in yellow needles, m. p. 87° (Found: N, 9·0. $C_{10}H_{11}ON$ requires N, 8·7%).

(12) 2 : 4-*Dinitrobenzaldehyde.*—Method (3*a*) was employed, using 2 g. of aldehyde in 3 c.c. of hot alcohol and 1 g. of β-methylhydroxylamine hydrochloride in 3 c.c. of alcohol. On mixing, heat was developed and after 30 minutes the yellow, crystalline precipitate was collected and crystallised from toluene, giving N-*methyl*-2 : 4-*dinitrobenzaldoxime*, yellow needles, m. p. 136° (Found: N, 18·9. $C_8H_7O_5N_3$ requires N, 18·7%).

With the exception of those containing nitro-groups, all the above *N*-ethers are readily soluble in water.

Hydrochlorides of N-*Ethers of Aldoximes.*

A solution of the *N*-ether in dry ether (or, in the case of those of *p*-nitro- and 6-nitro-3 : 4-methylenedioxy-benzaldoximes, in chloroform) was saturated with dry hydrogen chloride and the hydrochloride was immediately precipitated; this was collected, dried on a porous tile, the m. p. determined, a portion weighed and decomposed with 2*N*-sodium hydroxide for a halogen determination, and the rest decomposed with 2*N*-sodium carbonate solution. In all experiments of this type these operations were carried out as rapidly as possible. In the cases of *N*-methyl-*o*-, -*m*-, and -*p*-nitro- and -6-nitro-3 : 4-methylenedioxy-benzaldoximes, the precipitated solid obtained by treatment with sodium carbonate was found to be identical with the original *N*-ether by the method of mixed m. p.'s. If the minimum quantity of sodium carbonate solution was employed, *N*-methyl-*o*-methoxy- and -3 : 4-methylenedioxy-benzaldoximes separated in the hydrated form which, on keeping for a short time in a vacuum over solid sodium hydroxide, gave the original anhydrous compound. With *N*-methylbenzaldoxime and *N*-methyl-*p*-methoxybenzaldoxime, the soluble *N*-ethers were extracted from the sodium carbonate solution with chloroform, and the original *N*-ethers recovered by evaporation. Precipitation of the hydrochlorides from hot benzene solutions of the *N*-ethers gave similar results (compare Brady and Dunn, J., 1923, **123**, 1783).

The following hydrochlorides were prepared :

N-*Methyl*-o-*nitrobenzaldoxime hydrochloride*, a pale yellow, crystalline powder, m. p. 125—134° (decomp.) (Found : Cl, 16·8. $C_8H_9O_3N_2Cl$ requires Cl, 16·4%); N-*methyl*-m-*nitrobenzaldoxime hydrochloride*, a white, crystalline powder, m. p. 172—177° (decomp.) (Found : Cl, 16·9. $C_8H_9O_3N_2Cl$ requires Cl, 16·4%); N-*methyl*-p-*nitrobenzaldoxime hydrochloride*, a white, crystalline powder, m. p. 133—135° (decomp.) (Found : Cl, 14·7. $C_8H_9O_3N_2Cl$ requires Cl, 16·4%) [The low value for chlorine is due to the instability of this compound, which rapidly loses hydrogen chloride, turning to the yellow colour of the free *N*-ether; it is at once decomposed by water.]; N-*methylbenzaldoxime hydrochloride*, a white, crystalline powder, m. p. 131—136° (decomp. at 171°) (Found : Cl, 20·6. $C_8H_{10}ONCl$ requires Cl, 20·7%); on keeping in air, decomposition occurs and the odour of benzaldehyde soon becomes apparent; N-*methyl*-3 : 4-*methylenedioxybenzaldoxime hydrochloride*, a pale yellow, crystalline powder, m. p. 176—180° (decomp.) (Found : Cl, 16·9. $C_9H_{10}O_3NCl$ requires Cl, 16·5%); N-*methyl*-o-*methoxybenzaldoxime hydrochloride*, a white, crystalline powder, m. p. 70—100° (decomp. at 151°) (Found : Cl, 17·5. $C_9H_{12}O_2NCl$ requires Cl, 17·6%); N-*methyl*-p-*methoxybenzaldoxime hydrochloride*, a white, crystalline powder, m. p. 175—179° (decomp.) (Found : Cl, 18·2. $C_9H_{12}O_2NCl$ requires Cl, 17·6%); N-*methyl*-6-*nitro*-3 : 4-*methylenedioxybenzaldoxime hydrochloride*, a pale yellow, crystalline powder, m. p. 173—175° (decomp.) (Found : Cl, 13·7. $C_9H_9O_5N_2Cl$ requires Cl, 13·6%).

Action of Methyl Sulphate on Aldoximes.

Methyl sulphate (10 c.c.) and finely-powdered α-*o*-nitrobenzaldoxime (5 g.) were kept in a stoppered bottle in the dark for 8 months; a clear yellow solution was then obtained. Ether precipitated a yellow oil which solidified on cooling in a freezing mixture and scratching. After collecting, washing with dry ether, and drying between filter-paper, N-*methyl*-o-*nitrobenzaldoxime methosulphate* was obtained in practically theoretical yield as a pale yellow, crystalline powder, m. p. 99—107° (Found : N, 9·5; SO_4, 33·1. $C_9H_{12}O_7N_2S$ requires N, 9·6; SO_4, 32·9%). The methosulphate dissolved in 2*N*-sodium carbonate with evolution of carbon dioxide and separation of a yellow solid, which was found to be *N*-methyl-*o*-nitrobenzaldoxime; the alkaline solution, on digestion with concentrated hydrochloric acid and distillation, gave methyl alcohol, identified by oxidation to formaldehyde. N-*Methyl*-m-

nitrobenzaldoxime methosulphate, prepared in good yield similarly to the above, was a yellow, crystalline powder, m. p. 58—60° (Found : N, 9·0. $C_9H_{12}O_7N_2S$ requires N, 9·6%). α-*p*-Nitrobenzaldoxime slowly dissolves in methyl sulphate and bright yellow crystals of N-*methyl*-p-*nitrobenzaldoxime methosulphate* separate; m. p., after washing with ether, 85—91° (Found: N, 9·1. $C_9H_{12}O_7N_2S$ requires N, 9·6%). When both the *m*- and *p*-compounds are decomposed with 2*N*-sodium carbonate, the practically pure *N*-ether is precipitated. With α-benzaldoxime and methyl sulphate, colourless needles separated which, after collecting, washing with ether, and drying over solid sodium hydroxide, gave N-*methylbenzaldoxime methosulphate*, m. p. 60—63° (Found : N, 5·8. $C_9H_{13}O_5NS$ requires N, 5·7%). Treatment of this compound with sodium carbonate and extraction of the solution with chloroform gave *N*-methylbenzaldoxime; no trace of the characteristic odour of *O*-methylbenzaldoxime was observed in the mother-liquors from the methosulphate. α-*p*-Methoxybenzaldoxime dissolved slowly in methyl sulphate, and from the solution ether precipitated an oil which solidified only after a considerable time on scratching in a freezing mixture. After grinding the solid with ether and filtering, N-*methyl*-p-*methoxybenzaldoxime methosulphate* was obtained in good yield; white crystals, m. p. 89—90° (Found : N, 5·1. $C_{10}H_{15}O_6NS$ requires N, 5·1%). α-3 : 4-Methylenedioxybenzaldoxime slowly dissolved in methyl sulphate and large, colourless crystals separated; the mother-liquor went very dark owing, probably, to slight decomposition of the methylenedioxy-group. After collecting the solid and purifying by grinding with ether, an almost quantitative yield of N-*methyl*-3 : 4-*methylenedioxybenzaldoxime methosulphate* was obtained as colourless needles, m. p. 97—100° (Found : N, 4·9. $C_{10}H_{13}O_7NS$ requires N, 4·8%). In the last two cases, the corresponding *N*-ether was obtained by decomposing the methosulphates with sodium carbonate solution and extracting with chloroform. In the above results the reaction mixture was kept for 8 months, but decreasingly satisfactory yields were obtained in shorter times, and it was then necessary to precipitate the methosulphate with ether. The methyl sulphate must be free from acid; a sufficiently pure material can be obtained by shaking the commercial compound with two portions of 2*N*-sodium hydroxide for a minute, then with a little water, and drying with anhydrous potassium carbonate; distillation is not necessary.

Action of Methyl Iodide on α-Aldoximes.

(1) *α-Benzaldoxime.*—(*a*) The oxime (1 g.) was melted and mixed with methyl iodide (5 c.c.) and kept in a stoppered bottle in the

dark for 5 months. The brown crystals which had separated were collected, pressed on a porous tile, and washed with ether; they shrivelled at 65° and melted at 103°. On addition of 2*N*-sodium carbonate, carbon dioxide was evolved and the solution (after treatment with a few drops of sulphurous acid to remove iodine, and extraction with chloroform) gave 0·35 g. of *N*-methylbenzaldoxime, identified by a mixed m. p. and by hydrolysis. The remaining methyl iodide on evaporation gave no trace of the strong characteristic odour of *O*-methylbenzaldoxime.

(*b*) The oxime (5 g.) and methyl iodide (10 c.c.) were kept in the dark for 42 days; no crystals having separated, the brown solution was added to excess of ether, whereupon a brown solid separated, which was pressed on a porous tile and washed with ether, m. p. 73°; washing with acetone dissolved most of it, but a white solid remained which was apparently *N*-methylbenzaldoxime hydriodide: this darkened at 135° and melted at 150°; it was evidently impure (Found: I, 38·2. $C_8H_{10}ONI$ requires I, 48·3%). Carbon dioxide was liberated when this compound was treated with 2*N*-sodium carbonate, and chloroform extracted from the solution *N*-methylbenzaldoxime which was obtained pure on removing the solvent. On evaporating the ether–methyl iodide mixture, the odour of *O*-methylbenzaldoxime was absent.

(2) α-p-*Methoxybenzaldoxime*.—The finely-powdered oxime (5 g.) was added to methyl iodide (10 c.c.) and kept in a stoppered bottle in the dark for 28 days. The oxime slowly dissolved and was replaced by brownish needles of impure N-*methyl*-p-*methoxybenzaldoxime hydriodide* which, after being pressed on a porous tile and washed with ether, sintered at 131° and melted at 145° (Found: I, 30·5. $C_9H_{12}O_2NI$ requires I, 43·3%). Decomposition with sodium carbonate as with the previous compound, gave, on removing the chloroform, an oil from which crystals of *N*-methyl-*p*-methoxybenzaldoxime slowly separated; the residual oil contained *p*-methoxybenzaldehyde, due to partial hydrolysis of the *N*-ether—a common experience with this particular compound. In a second experiment, the brown solid was washed with acetone and a white, crystalline material remained, m. p. 155—159° (Found: I, 29·1%), whilst in a third similar experiment the product had m. p. 160° and appeared to be a *compound* of 2 mols. of the *N*-ether and 1 mol. of hydrogen iodide (Found: N, 6·7; I, 28·4. $2C_9H_{11}O_2N,HI$ requires N, 6·1; I, 27·7%). A determination of the amount of β-methylhydroxylamine formed on hydrolysis of this compound with hydrochloric acid gave 20·1% (Calc., 20·0%). The product on reaction with sodium carbonate gave *N*-methyl-*p*-methoxybenzaldoxime in a fairly pure condition. Again no indication of the

presence of the characteristic odour of *O*-methyl-*p*-methoxybenzaldoxime was observed from the methyl iodide mother-liquors in any of the experiments.

(3) α-o-*Methoxybenzaldoxime.*—The oxime (2 g.) in methyl iodide (10 c.c.) was kept as before for 25 days; it slowly dissolved and was replaced by long clusters of yellow needles with some darker crystals; these were collected, washed with ether, and the dark brown crystals removed by hand. The lighter-coloured product, m. p. 137° (Found : I, 41·7%), with sodium carbonate, as before, gave *N*-methyl-*o*-methoxybenzaldoxime. The methyl iodide solution on evaporation yielded a considerable amount of unchanged oxime. A second preparation was kept for 11 months and the crystals were washed with ether and acetone, N-*methyl*-o-*methoxybenzaldoxime hydriodide* being obtained as a lemon-yellow, crystalline powder, m. p. 142° (decomp.) (Found : I, 42·3. $C_9H_{12}O_2NI$ requires I, 43·3%).

(4) β-*Cinnamaldoxime.*—The oxime (2 g.) in methyl iodide (5 c.c.) was kept for 5 weeks; it slowly dissolved and was replaced by light brown crystals of N-*methylcinnamaldoxime hydriodide*, which were washed with ether, m. p. 71—79° (Found : I, 41·3. $C_{10}H_{12}ONI$ requires I, 43·9%). On decomposition with sodium carbonate, *N*-methylcinnamaldoxime was formed.

No satisfactory method of crystallising these hydriodides has been discovered. No appreciable reaction occurred between methyl iodide and α-*m*-nitro-, -*p*-nitro-, and -3 : 4-methylenedioxy-benzaldoximes in 3 months.

Action of Methyl Sulphate on Solutions of α-Aldoximes in Sodium Hydroxide.

The following methylations were carried out under similar conditions with the view of obtaining some idea of the relative amounts of *O*- and *N*-ethers formed from various aldoximes. In some cases methylation was incomplete with the limited amount of methyl sulphate employed, and difficulties of manipulation frequently resulted in loss of material; this was particularly marked in the case of the *N*-ethers, since, owing to the presence of traces of acid or alkali, distillation in steam sometimes caused considerable hydrolysis. The weights of ethers recorded are of the crude products unless otherwise stated, but in every case the compounds were subsequently purified and their identity was established by mixed m. p.'s.

Method 1. α-*o*-Nitrobenzaldoxime (10 g.), dissolved in 2*N*-sodium hydroxide (35 c.c.), was shaken at 20—25° for 15 minutes with methyl sulphate (6 c.c.). The mixture was extracted four times with chloroform, water (50 c.c.) was added to the extract, and the whole distilled in steam; after the chloroform had passed over, the *O*-ether solidified in the condenser and was melted out from time to time; at the end of 2 hours no more *O*-ether distilled. After separating the chloroform from the distillate, the aqueous layer was extracted with a further quantity of chloroform and evaporation of the combined extracts gave *O*-methyl-*o*-nitrobenzaldoxime (7·0 g.). Extraction of the solution in the flask gave *N*-methyl-*o*-nitrobenzaldoxime (1·9 g.). The mother-liquor from the methylation, after acidification and extraction with chloroform, gave the unmethylated oxime (1·0 g.). In a similar way, α-*m*-nitrobenzaldoxime gave 6·7 g. of *O*-methyl ether and 0·6 g. of *N*-methyl ether. If during the methylation the temperature is allowed to rise, or if the mixture is left for too long, the solution becomes reddish-brown, due to hydrolysis of the *N*-ether and reduction of the nitro-group by the alkaline β-methylhydroxylamine.

Equivalent quantities of α-*o*- and -*p*-methoxy-, -*p*-chloro-, and -3 : 4-methylenedioxy-benzaldoximes were methylated in a similar manner. 4·5 G. of α-*o*-methoxybenzaldoxime gave 3·3 g. of α-O-*methyl*-o-*methoxybenzaldoxime*, a pleasant-smelling, colourless oil, b. p. 241°/761 mm., 138—139°/25 mm. (Found : N, 8·4. $C_9H_{11}O_2N$ requires N, 8·5%), 1·4 g. of *N*-methyl ether, and 0·03 g. of unchanged oxime. 9·0 G. of α-*p*-methoxybenzaldoxime gave 5·9 g. of *O*-methyl ether, 2·3 g. of *N*-methyl ether, and 0·7 g. of unchanged oxime. 9·0 G. of α-*p*-chlorobenzaldoxime gave 7·5 g. of α-O-*methyl*-p-*chlorobenzaldoxime*, colourless needles, m. p. 28° (Found : N, 8·3. C_8H_8ONCl requires N, 8·3%), 1·3 g. of *N*-methyl ether, and 0·1 g. of unchanged oxime. 10 G. of α-3 : 4-methylenedioxybenzaldoxime gave 6 g. of *O*-methyl ether and 0·6 g. of *N*-methyl ether; the *O*-ether solidified slowly and, after pressing on a porous tile and crystallising from dilute alcohol, pure α-O-*methyl*-3 : 4-*methylenedioxybenzaldoxime* was obtained as white, nacreous plates, m. p. 37° (Found : N, 7·9. $C_9H_9O_3N$ requires N, 7·8%). A somewhat larger quantity of benzaldoxime was employed for methylation : 35 g. gave 16 g. of redistilled *O*-methyl ether and 7·2 g. of *N*-methyl ether.

In two cases, a somewhat different procedure had to be adopted owing to the insolubility of the sodium salts. α-*p*-Nitrobenzaldoxime (10 g.) was added to 2*N*-sodium hydroxide (25 c.c.); it dissolved, but the sodium salt soon crystallised; water was added (25 c.c.), and then methyl sulphate (6 c.c.); the liquid became very thick and could not be shaken, so a further 25 c.c. of sodium hydroxide and 50 c.c. of water were added. After 5 minutes, the mixture was filtered and the solid washed with water and distilled in steam. From the distillate, 7·6 g. of practically pure *O*-methyl ether were obtained and the orange solution in the flask deposited 1·0 g. of nearly pure *N*-methyl ether on cooling. α-6-Nitro-3 : 4-methylenedioxybenzaldoxime (10 g.) was dissolved in dilute sodium hydroxide (75 c.c. of 2*N*; 250 c.c. of water) and methyl sulphate (8 c.c.) added; on shaking, a solid soon separated and was collected after 5 minutes, the filtrate (*A*) being preserved. The solid was divided into two parts, (*B*) and (*C*). (*B*) was distilled in steam and a crystalline solid slowly passed over, which on crystallising from alcohol gave α-O-*methyl*-6-*nitro*-3 : 4-*methylenedioxybenzaldoxime* in yellow needles, m. p. 147° (Found : N, 12·7. $C_9H_8O_5N_2$ requires N, 12·5%). After 6 hours' distillation, the solid remaining in the flask melted at 140—147° and one crystallisation gave the pure *O*-ether. The solid (*C*) was fractionally crystallised from alcohol and was found to consist almost entirely of *O*-ether, but a very small quantity of impure *N*-ether was isolated from the more soluble fractions. The filtrate (*A*) slowly deposited more *O*-ether, which was separated and the filtrate extracted with chloroform; on removing the solvent and crystallising the residue from alcohol, a small amount of *N*-ether was obtained.

Method 2. The methylation was carried out as before, but the reaction mixture was extracted several times with ether, and the extract, after drying with anhydrous sodium sulphate, was saturated with dry hydrogen chloride. The precipitated hydrochloride of the *N*-ether was decomposed with dilute sodium carbonate solution and the *N*-ether extracted with chloroform. The ethereal solution was washed with water and, on drying and evaporating, it gave the *O*-ether. 10 G. of α-*p*-methoxybenzaldoxime gave 5·9 g. of *O*-ether and 2·1 g. of *N*-ether; 10 g. of α-3 : 4-methylenedioxybenzaldoxime gave 7·7 g. of *O*-ether and 0·4 g. of *N*-ether; 10 g. of α-*m*-nitrobenzaldoxime gave 7 g. of *O*-ether and 1·1 g. of *N*-ether.

Action of Methyl Sulphate on Solutions of β-Aldoximes in Sodium Hydroxide.

Previous workers have shown that the methylation of the β-aldoximes in methyl alcohol with sodium methylate and methyl iodide gives mainly the *N*-ether. The use of methyl sulphate with a solution of the β-aldoxime in aqueous sodium hydroxide is not very satisfactory as a guide to the relative quantities of the two ethers formed; in some cases, the sodium salt crystallises out, and in others trouble is caused by the hydrolysis of the *N*-ether. In order to avoid the presence, after the reaction, of unchanged oxime, which, owing to its feeble acidity, would be extracted by solvents from the alkaline solution, some excess of methyl sulphate is desirable; unfortunately, any of this which may be undecomposed passes into the chloroform extract and is hydrolysed during the steam-distillation, the resulting acid then hydrolysing the *N*-ether.

β-m-*Nitrobenzaldoxime.*—The oxime (7·3 g.) in 2*N*-sodium hydroxide (35 c.c.) was treated in the same way as the α-oxime with methyl sulphate (6 c.c.); the ethers were extracted with chloroform and distilled in steam. From the distillate, 2·8 g. of β-*O*-methyl-*m*-nitrobenzaldoxime, m. p. 57°, were obtained, the low m. p. being probably due to contamination with *m*-nitrobenzaldehyde from the hydrolysis of the *N*-ether. The residue in the flask gave, on extraction with chloroform, 4·6 g. of *N*-methyl-*m*-nitrobenzaldoxime.

β-p-*Methoxybenzaldoxime.*—Chloroform extraction and distillation in steam resulted in much hydrolysis of the *N*-ether; the β-oxime (4·5 g.) in 2*N*-sodium hydroxide (75 c.c.) was therefore methylated with methyl sulphate (4·5 c.c.). The emulsion obtained was extracted with ether (25 c.c.), in which the *O*-methyl ether is readily soluble. The ethereal layer was treated as before in order to produce the hydrochloride of the *N*-ether; yield 0·32 g., corresponding to 0·26 g. of *N*-ether. The filtrate from the hydrochloride was neutralised by sodium carbonate and on evaporation gave 0·41 g. of α-*O*-methyl-*p*-methoxybenzaldoxime, formed from the β-*O*-methyl ether by the hydrogen chloride. The original aqueous layer from the ether-extraction was extracted repeatedly with chloroform and, on evaporating the solvent, 3·42 g. of *N*-ether were obtained. From 4·5 g. of β-oxime there were therefore isolated 3·68 g. of *N*-ether and 0·41 g. of *O*-ether.

β-3 : 4-*Methylenedioxybenzaldoxime.*—Steam distillation of the chloroform extract as before gave large quantities of the aldehyde, but satisfactory results were obtained by the following method: A solution of the oxime (5 g.) in 2*N*-sodium hydroxide (80 c.c.) was treated with methyl sulphate (5 c.c.), shaken, with cooling under the tap, for 15 minutes, and then cooled in ice; most of the *N*-ether crystallised out, and was collected, washed with a little ice-water and then with ether, in which the *O*-ether is readily but the *N*-ether sparingly soluble. The *N*-ether, after dehydration in a vacuum over calcium chloride, weighed 3·75 g. The filtrate and washings, both aqueous and ethereal, were mixed and extracted twice with 25 c.c. of ether. The extract on being subjected to the usual process yielded 0·05 g. of the hydrochloride of the *N*-ether, corresponding to 0·04 g. of *N*-ether itself. A further 0·62 g. of *N*-ether was obtained from the aqueous portion by extraction with chloroform, making a total yield of 4·4 g. of *N*-ether. The ethereal extract, after treatment with solid sodium carbonate (to remove acid) and evaporation, gave 0·34 g. of an oil consisting of the α-*O*-ether mixed with a little aldehyde, the former being produced by the action of the hydrogen chloride on the β-*O*-ether.

The methylation of the β-oximes without isolation of the oxime gave interesting results. A solution of α-*m*-nitrobenzaldoxime (5 g.) in dry chloroform was saturated with dry hydrogen chloride, the precipitated hydrochloride collected, pressed on a porous plate until free from chloroform, dissolved as rapidly as possible in 150 c.c. of 2*N*-sodium hydroxide, and the solution shaken for some minutes with methyl sulphate (5 g.), cooling under the tap. The solid was separated, washed with a little water, and distilled in steam. From the distillate almost pure β-*O*-methyl-*m*-nitrobenzaldoxime (m. p. 71—74°) crystallised; as the pure compound has m. p. 74°, the m. p. of the product indicates that practically no α-*O*-ether was present and consequently that there was little α-*m*-nitrobenzaldoxime in the alkaline solution. It appears, therefore, that the presence of a considerable amount of the α- in the β-oxime obtained by decomposing the hydrochloride in the usual way is due to isomeric change occurring during manipulation subsequent to the decomposition of the hydrochloride rather than to the hydrochloride being a mixture. The residual solution in the flask deposited almost pure *N*-ether on cooling. The yield of *N*-ether was greater than that of *O*-ether.

The hydrochloride from α-*p*-nitrobenzaldoxime (6 g.), obtained as before, was dissolved in 2*N*-sodium hydroxide (200 c.c.) and treated with methyl sulphate (10 g.). On collecting the ethers formed, washing, and distilling in steam, the aqueous solution in the flask on cooling deposited 3·5 g. of nearly pure *N*-ether, and 0·3 g. of the β-*O*-ether (m. p. 69—70°) crystallised from the distillate. Fractionation of this ether gave two fractions of m. p. 70°, and a third, m. p. 69°. The m. p. of the pure β-*O*-methyl ether is 70°, but it is raised by admixture with the α-*O*-ether, so there is not the same criterion of purity as with the *m*-nitro-compound (compare Brady and Dunn, J., 1913, **103**, 1625), but it seems probable that the alkaline solution from the hydrochloride was practically free from the α-oxime. The purity of the β-oxime-forming hydrochlorides in the case of *m*- and *p*-nitrobenzaldoximes is in accordance with expectation, since it has been shown that in these cases the α-oxime-forming hydrochlorides are stable only at very low temperatures (Brady and Dunn, J., 1916, **109**, 680; 1923, **123**, 1798).

Action of Methyl Iodide and Sodium Methoxide on α-o-, -m-, *and* -p-*Nitrobenzaldoximes.*

The oxime (5 g.) was dissolved in methyl alcohol, a solution of sodium (1 g.) in methyl alcohol added followed by methyl iodide

(7 g.), and the mixture kept at room temperature for 3 days. Water was added and the precipitated yellow solid distilled in steam. From the distillate the *O*-methyl ethers crystallised almost pure; the liquor remaining in the flask was evaporated on the water-bath and the residue crystallised from alcohol, giving a small amount of pure *N*-ether in each case.

Action of Methyl Iodide and Silver Oxide on Aldoximes.

α-m-*Nitrobenzaldoxime.*—A mixture of the oxime (5 g.), dry silver oxide (10 g.), and methyl iodide (20 c.c.) was heated under reflux for 30 minutes; ether was added and, after filtering, the ether and excess of methyl iodide were removed by a current of dry air. The yellow residue was washed with cold 2*N*-sodium hydroxide, which dissolved any excess of oxime and the *N*-ether, and one crystallisation of the residue from dilute alcohol gave 3·8 g. of pure α-*O*-methyl-*m*-nitrobenzaldoxime; by extracting the alkaline washings with chloroform, 0·4 g. of *N*-methyl-*m*-nitrobenzaldoxime was obtained.

β-m-*Nitrobenzaldoxime.*—The oxime (6 g., m. p. 113—118°) and dry silver oxide (12 g.) were added to methyl iodide (40 c.c.) and considerable heat was evolved; after heating under reflux for 45 minutes, ether was added and the filtered solution evaporated in a current of air. The crude residue was extracted with hot light petroleum and from the extract 1·2 g. of pure β-*O*-methyl-*m*-nitrobenzaldoxime crystallised. The residue insoluble in the petroleum and the silver oxide and iodide residues were extracted with boiling benzene and on evaporating to small bulk 0·2 g. of pure *N*-methyl-*m*-nitrobenzaldoxime crystallised. In a second experiment, 2 g. of oxime gave 1·1 g. of pure β-*O*-ether and some *N*-ether.

β-3-*Nitro*-p-*methoxybenzaldoxime.*—The oxime (2 g.), dry silver oxide (4 g.), and methyl iodide (20 c.c.) were boiled under reflux for an hour; ether was added and, after filtering, the solution was evaporated in a current of air and the residue distilled in steam; the *O*-ether passed over slowly and crystallised in the distillate; recrystallisation from alcohol gave β-O-*methyl*-3-*nitro*-p-*methoxybenzaldoxime* as very pale yellow-green plates, m. p. 135° (Found: N, 13·7. $C_9H_{10}O_4N_2$ requires N, 13·3%). A mixture of about equal parts of this compound and α-*O*-methyl-3-nitro-*p*-methoxybenzaldoxime (m. p. 120°) had m. p. 103—110°. After hydrogen chloride had been passed into an ethereal solution of the β-*O*-ether, evaporation in a current of air showed that complete conversion to the α-*O*-methyl ether had occurred.

The Action of Alkalis on Methyl Ethers.

Boiling 2*N*-sodium hydroxide has no appreciable action on the *O*-methyl ethers; with the *N*-ethers of, *e.g.*, benzaldoxime or *p*-methoxybenzaldoxime, on gentle warming an oil began to separate and the odour of the aldehyde was obvious. After 5 minutes on the water-bath, the solution was cooled and extracted with ether; the aqueous solution immediately reduced cold Fehling's solution, indicating the presence of β-methylhydroxylamine; the ethereal solution was evaporated and the resulting oil treated with semicarbazide hydrochloride and sodium acetate, whereupon an amount of the semicarbazone of benzaldehyde or *p*-methoxybenzaldehyde was obtained corresponding approximately with the quantity of *N*-ether used. Where a nitro-group was present, *e.g.*, with *N*-methyl-*m*-nitrobenzaldoxime, tarry products were obtained, owing probably to the reducing action of the β-methylhydroxylamine liberated.

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