

LXXXIV.—*The Isomerism of the Oximes.\* Part III.*  
*The Hydroxybenzaldoximes.*

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THE authors have for some time been engaged on a detailed investigation of the three hydroxybenzaldoximes and their derivatives: much of the earlier work on these compounds has proved untrustworthy, and it has been found necessary to repeat and amplify it.

Of the oximes themselves, *o*-hydroxybenzaldoxime or salicylaldoxime calls for no special comment, but the para- and meta-compounds require some mention. *p*-Hydroxybenzaldoxime was described by Lach (*Ber.*, 1883, **16**, 1782), who stated that it melted at 65°, and published an analysis agreeing with the formula  $C_7H_7O_2N$ . Dollfuss, however (*Ber.*, 1892, **25**, 1924), showed that the compound obtained by Lach, and melting when pure at 72–73°, contained water, and that the anhydrous oxime melted at 112°; he did not, however, state the amount of water in the hydrated variety. The authors have been able to show that the oxime melting at 72° contains 1 molecule of water of crystallisation, which it retains even after recrystallising from non-aqueous

\* The authors regret that in the previous paper on this subject no mention was made of the work of Patterson and McMillan on the rate of transformation of *syn*- into *anti*-oximes in ethyl tartrate solution (*Proc. Phil. Soc. Glasgow*, 1911).

solvents, but is lost on drying over potassium hydroxide in a vacuum, giving the oxime melting at  $112^{\circ}$ .

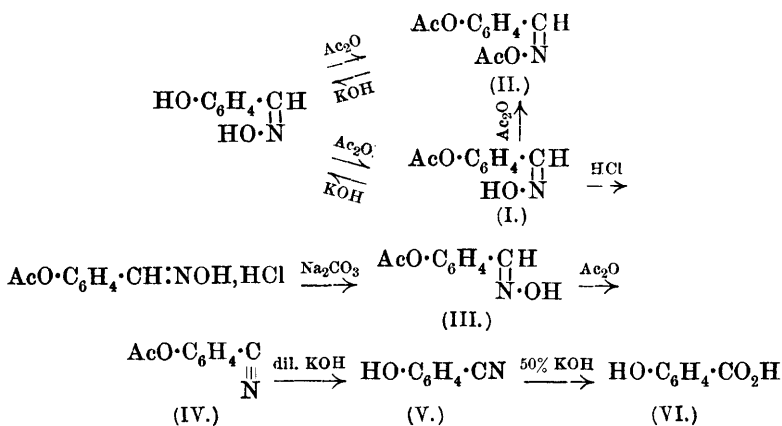
*m*-Hydroxybenzaloxime is described in the literature as melting at  $87^{\circ}$ , but Jowett (T., 1900, **77**, 710) states that, after several recrystallisations from benzene, an isomeric compound melting at  $138^{\circ}$  could be obtained. Jowett did not continue the investigation and as this was possibly the first case in which a hydroxybenzsynaldoxime had been isolated, the work has been repeated. After five recrystallisations from benzene, the melting point of the oxime rose to  $90^{\circ}$ , but another five recrystallisations produced no further change. The product on treatment with acetic anhydride gave an acetyl derivative identical with that obtained from the starting material. In view of the error of Lach in overlooking the water of crystallisation in the para-compound, the oxime was analysed, and shown to be anhydrous. (Found, C=61.1; H=5.2. Calc., C=61.3; H=5.1 per cent.) Prolonged boiling with benzene under reflux had no effect on the melting point of the oxime. Jowett's result cannot, therefore, be confirmed.

In view of the important part played by the acetyl derivatives in the determination of the configuration of oximes, it was thought desirable to prepare these compounds, especially as the possibility that the hydrated and anhydrous *p*-hydroxybenzaloximes might be different forms does not seem to have been considered. Lach (*loc. cit.*) mentions a diacetyl derivative of salicylaloxime, which, however, in a subsequent paper (*Ber.*, 1884, **17**, 1572) he showed to be *o*-acetoxybenzonitrile. Dollfuss (*loc. cit.*) describes monoacetyl derivatives of *m*- and *p*-hydroxybenzaloximes. The fact that these compounds on hydrolysis regenerated the original oxime has been taken as establishing that the oximes existed in the *anti*-form; the possibility that the phenolic and not the oximino-group had been acetylated does not seem to have occurred to previous workers, and as the position of the acetyl group has not been proved, their deductions as regards the configuration of the oximes from a study of these compounds are not justified.

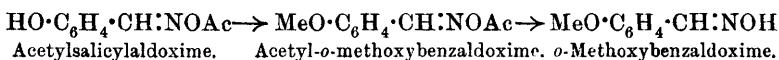
The action of acetic anhydride on *p*-hydroxybenzaloxime proved to be of unusual interest; if either the hydrated or the anhydrous oxime is dissolved in acetic anhydride, and the mixture left over calcium hydroxide and concentrated sulphuric acid in a vacuum, a monoacetyl derivative (I), identical with that of Dollfuss, is obtained, melting at  $114$ – $115^{\circ}$ ; if, however, a solution of hydrated or anhydrous oxime, or of the monoacetyl derivative, in acetic anhydride is treated with sodium carbonate solution, a diacetyl derivative (II), melting at  $82^{\circ}$ , is formed. That both the hydrated and anhydrous oxime yield a diacetyl derivative, and not

$$\text{HO}\cdot\text{C}_6\text{H}_4\cdot\text{CH}:\text{NOAc}$$

has the constitution  $\text{AcO} \cdot \text{C}_6\text{H}_4 \cdot \text{CH} \cdot \text{NOH}$ , that is, is *p*-acetoxybenzaldoxime. If this substance is dissolved in anhydrous ether and saturated with dry hydrogen chloride, a hydrochloride is precipitated, which on decomposition with sodium carbonate solution yields a compound melting at  $132^\circ$ , and proving to be *p*-acetoxybenzsynaldoxime (III). On treatment with acetic anhydride it gives *p*-acetoxybenzonitrile (IV), and on treatment with alkali hydroxide *p*-hydroxybenzonitrile (V), and, finally, *p*-hydroxybenzoic acid (VI). The course of these reactions is as follows:



Monoacetyl derivatives of *o*- and *m*-hydroxybenzaldoximes have also been prepared, the meta-compound being identical with that of Dollfuss; there is, however, no evidence of the formation of diacetyl derivatives. Solutions of these acetyl compounds in dry ether give a precipitate with hydrogen chloride after prolonged treatment, but this proved in each case to be the hydrochloride of the original hydroxybenzaldoxime, the acetyl group having been removed. It seemed likely that in these cases, in distinction to the para-compound, the oximino-group was acetylated. In order to acquire further evidence on this point, the acetyl derivative of salicylaldoxime was methylated, and the product proved to be acetyl-*o*-methoxybenzaldoxime, yielding on hydrolysis *o*-methoxybenzaldoxime. This establishes the position of the acetyl-group:



Since by acting on salicylaldoxime with acetic anhydride and sodium carbonate the oximino-group is acetylated instead of a nitrile being formed, it follows that salicylaldoxime must possess the *anti*-configuration.

*o*-Acetoxybenzaldoxime,  $\text{AcO} \cdot \text{C}_6\text{H}_4 \cdot \text{CH} : \text{NOH}$ , and the acetyl derivatives of *m*-hydroxybenzaldoxime are being investigated; the acetyl derivative of *m*-hydroxybenzaldoxime has not been methylated, as *m*-methoxybenzaldoxime has not been described. The authors hope to deal with this in a further communication.

Whilst many substituted benzaldoximes have been shown to exist in the two isomeric forms, *anti* and *syn*, it is noteworthy that no evidence of the existence of a second isomeride has been obtained in the case of any of the hydroxybenzaldoximes. The authors have tried various methods under varying conditions to bring about the conversion, but so far without success. There seems to be no satisfactory reason for this failure, and, indeed, the conditions deciding the existence of a second isomeride are very little understood. Substitution in the ortho-position seems to hinder isomeric change; *o*-chlorobenz*syn*aldoxime and *o*-nitrobenz*syn*aldoxime have been obtained; *o*-methoxybenzaldoxime, however, cannot be converted by ordinary means into the *syn*-form, although the para-compound offers no difficulty; the amino-benzaldoximes have not been thoroughly investigated, but the authors have found that *o*-aminobenzaldoxime cannot be transformed into a second isomeride in the usual way. The different behaviour on acetylation of the *o*- and *p*-hydroxybenzaldoximes rather indicates that ortho-substitution influences the basicity of the oximino-group, which may have some bearing on the problem.

It seems questionable whether any purely stereochemical reasons can be advanced to account for the ease or otherwise with which the *syn*-isomerides can be obtained; benzaldoxime substituted in the para-position by the halogens, or by the nitro-, cyano-, methyl, methoxy-, ethoxy-, or acetoxy-group can be obtained in the two isomeric forms, whereas *p*-hydroxybenzaldoxime apparently only exists as the *anti*-compound.

In view of the instability of the *syn*-aldoximes in the presence of acids, it is possible that the hydrogen ion of the phenolic group may play some part in the prevention of the formation of the *syn*-isomeride; it is noteworthy that there is no case in which an aldoxime containing the possibility of an ionisable hydrogen atom has been shown to exist in the two forms.

## EXPERIMENTAL.

*Preparation of the Hydroxybenzaloximes.*

The oximes were prepared in the usual way by dissolving the aldehyde in alcohol, adding two equivalents of sodium hydroxide dissolved in a little water, and one equivalent of hydroxylamine hydrochloride, also in water. After remaining for twenty-four hours the solution was diluted, carbon dioxide passed in to decompose the sodium salt, and the oxime extracted with ether. The ether was removed at room temperature, and the residue recrystallised. In the case of salicylaldoxime, the most convenient method of purification was found to consist in dissolving in benzene, cooling in ice, and adding previously cooled light petroleum with constant stirring; the *m*-hydroxybenzaloxime is best purified by two or three recrystallisations from benzene. The crude *p*-hydroxybenzaloxime contains water of crystallisation; part was recrystallised from a very little water, and the rest dried in a vacuum over potassium hydroxide, and the product recrystallised from anhydrous chloroform. The hydrated oxime melted at 72°:

0.1186 gave 0.2340 CO<sub>2</sub> and 0.0648 H<sub>2</sub>O. C=53.8; H=6.1.

0.3787 lost 0.0444. H<sub>2</sub>O=11.7.

C<sub>7</sub>H<sub>7</sub>O<sub>2</sub>N.H<sub>2</sub>O requires C=54.2; H=5.8; H<sub>2</sub>O=11.6 per cent.

The compound remaining after dehydration melted at 112°:

0.1274 gave 0.2845 CO<sub>2</sub> and 0.0605 H<sub>2</sub>O. C=60.9; H=5.2.

C<sub>7</sub>H<sub>7</sub>O<sub>2</sub>N requires C=61.3; H=5.1 per cent.

*The Acetyl Derivatives of the Hydroxybenzaloximes.*

These compounds were obtained by treating the oximes with excess of acetic anhydride, warming gently, and allowing to remain for ten minutes; the excess of acetic anhydride was decomposed by shaking with sodium carbonate solution, and the solid acetyl derivative was collected and recrystallised. *Acetylsalicylaldoxime* is best recrystallised from acetone and water, and forms pale pink crystals, melting at 69°:

0.1828 gave 12.0 c.c. N<sub>2</sub> at 18° and 756 mm. N=8.0.

C<sub>9</sub>H<sub>9</sub>O<sub>3</sub>N requires N=7.8 per cent.

The meta-compound is identical with that obtained by Dollfuss (*loc. cit.*), and melts at 113°. (Found, N=7.6. Calc., N=7.8 per cent.)

*Diacetyl-p-hydroxybenzaloxime* crystallises from acetone and water in pearly scales, melting at 81°:

0.1000 gave 0.2196  $\text{CO}_2$  and 0.0452  $\text{H}_2\text{O}$ .  $\text{C}=59.8$ ;  $\text{H}=5.0$ .

0.2116 „ 12 c.c.  $\text{N}_2$  at  $19^\circ$  and 765 mm.  $\text{N}=6.6$ .

$\text{C}_{11}\text{H}_{11}\text{O}_4\text{N}$  requires  $\text{C}=59.7$ ;  $\text{H}=4.9$ ;  $\text{N}=6.3$  per cent.

It was found that the hydrated oxime also yielded this diacetyl derivative.

In the case of the *o*- and *m*-hydroxybenzaloximes, the same acetyl compounds were obtained if the oximes were dissolved in a minimum excess of acetic anhydride and left over calcium hydroxide and concentrated sulphuric acid in a vacuum; if, however, *p*-hydroxybenzaloxime is treated in this way, the monoacetyl derivative is obtained, melting at  $114\text{--}115^\circ$  (compare Dollfuss, *loc. cit.*).

#### *Action of Hydrogen Chloride on the Acetyl Derivatives of the Hydroxybenzaloximes.*

The acetyl derivatives were dissolved in dry ether, the mixture cooled in ice, and saturated with dry hydrogen chloride. The ortho-compound after some time yielded a pale yellow precipitate, which was rapidly collected, and more hydrogen chloride passed into the filtrate. After some time a red precipitate was formed, which was also collected. The yellow compound was decomposed with sodium carbonate solution, an oily product being formed, which was extracted with ether. After removing the ether, an oil was obtained, which solidified on cooling; it was recrystallised from benzene and light petroleum, and proved to be salicylaloxime. The red compound yielded a red, gummy mass on treatment with sodium carbonate, which on pressing on a porous plate left a red solid; this, and the similar compound obtained from the acetyl derivative of *p*-hydroxybenzaloxime (see below), is being further investigated. The acetyl derivative of *m*-hydroxybenzaloxime behaved in much the same way, except that no coloured compound could be obtained. The precipitated hydrochloride on treatment with sodium carbonate solution completely dissolved, and on extracting the solution with ether, *m*-hydroxybenzaloxime (m. p.  $87^\circ$ ) was obtained. According to Luxmoore (T., 1896, **69**, 189), "when dry hydrogen chloride is passed into a cooled ethereal solution of acetylbenzantialdoxime, benzonitrile is formed as stated by Minunni (*Gazzetta*, 1892, **22**, ii, 174); in many cases benzamide is also obtained, and sometimes a hydrochloride of benzamide is precipitated." The authors have repeated this experiment, but have found that the reaction proceeds in the same manner as in the case of the acetyl derivative of salicylaloxime. After some minutes a white precipitate was obtained; this was collected,

and proved to be a hydrochloride, and was decomposed with sodium carbonate solution.

The residue was completely soluble in dilute alkali hydroxide, and the solution evolved no ammonia on boiling. After one recrystallisation from benzene it melted at  $129^{\circ}$ , mixed with benzsynaldoxime at  $130^{\circ}$ , and with benzamide at  $90-95^{\circ}$ .

The ethereal solution from which the hydrochloride was separated was washed with water and sodium hydroxide solution to remove hydrogen chloride, acetic acid, and any benzaldoxime present and the ether evaporated. The residue consisted of a small quantity of oil, which solidified slowly, but was insufficient to admit of further examination; there was, however, no odour of benzonitrile. Hence the main reaction consists in the elimination of the acetyl group and formation of the hydrochloride of benzaldoxime.

The monoacetyl derivative of *p*-hydroxybenzaldoxime, when treated as above, gave more readily a pale pink precipitate (I), which was collected; the mother liquor, on remaining on ice, deposited a dark red compound (II), soluble in sodium carbonate to a deep orange solution, from which acids reprecipitated the red substance. The first-formed hydrochloride (I) was decomposed with sodium carbonate solution, and the white solid remaining was collected, the filtrate on extraction with ether yielding a small quantity of *p*-hydroxybenzaldoxime. The solid was recrystallised from dilute alcohol, when it separated in shining plates, melting at  $131^{\circ}$ :

0.1030 gave 0.2274  $\text{CO}_2$  and 0.0482  $\text{H}_2\text{O}$ .  $\text{C}=60.2$ ;  $\text{H}=5.2$ .

$\text{C}_9\text{H}_9\text{O}_3\text{N}$  requires  $\text{C}=60.3$ ;  $\text{H}=5.0$  per cent.

This compound, *p*-acetoxybenzsynaldoxime, on hydrolysis with alkalis, yielded acetic acid and *p*-hydroxybenzaldoxime. On treating with acetic anhydride at  $30^{\circ}$ , decomposing the reaction mixture with sodium carbonate solution, and extracting with ether, a compound was obtained from the ethereal solution which proved to be *p*-acetoxybenzonitrile from its melting point ( $57^{\circ}$ ) and mixed melting point with that substance. The compound so obtained was hydrolysed to *p*-hydroxybenzonitrile (m. p.  $113^{\circ}$ ) by warming with dilute alkali, and finally, by using 50 per cent. alkali, to ammonia and *p*-hydroxybenzoic acid (m. p.  $210^{\circ}$ ).

In connexion with the determination of the position of the acetyl group in the acetyl derivative of salicylaldoxime, it has been necessary to prepare *o*-methoxybenzaldoxime and its acetyl derivative. An attempt was made to prepare a *syn*-derivative of the former by the action of dry hydrogen chloride in dry ether, but the hydrochloride so obtained regenerated the original oxime on treatment

with sodium carbonate solution. The melting point of acetyl-*o*-methoxybenzaloxime, prepared by either of the methods previously described for acetylsalicylaloxime (see above), was 52°, which is 12° higher than that given in the literature (Dollfuss, *Ber.*, 1892, 25, 1924).

*Methylation of the Acetyl Derivative of Salicylaloxime.*

The acetyl derivative of salicylaloxime was dissolved in ether, and a slight excess of methyl iodide added, and excess of dry silver oxide. The mixture was shaken from time to time, and finally left overnight; after filtering and removing the ether and excess of methyl iodide on the water-bath, an oily substance remained. A portion of this oil was left over calcium chloride in a vacuum for some days, and then cooled in a freezing mixture of ice and calcium chloride, when a crystalline substance separated. This was dried, and after recrystallisation melted at 51°, and did not depress the melting point of acetyl-*o*-methoxybenzaloxime prepared from *o*-methoxybenzaloxime. The rest of the oil was boiled for some minutes with 2*N*-alkali, and the solution acidified and extracted with ether; from the ethereal solution was obtained a small quantity of *o*-methoxybenzaloxime, identified by its melting point (82°) and mixed melting point with a specimen of that compound prepared from *o*-methoxybenzaldehyde.

*Attempts to Prepare the Hydroxybenzsynaldoximes.*

The authors have attempted to prepare the hydroxybenzsynaldoximes by the usual methods. The oximes were dissolved in anhydrous ether, and dry hydrogen chloride passed into the solution; a copious, white precipitate of a hydrochloride was formed in each case, which was collected and dried. The hydrochloride of salicylaloxime has been described by Lach (*loc. cit.*), but he omits to give the melting point, which was found to be 152° (with decomposition). The hydrochlorides of the *m*- and *p*-hydroxybenzaloximes are described by Dollfuss (*loc. cit.*), who did not, however, analyse them. (Found, Cl = 20.0, 20.3. Calc., 20.4 per cent.) The hydrochlorides were, in the first experiments, decomposed with dilute sodium carbonate solution, and in the case of the last-mentioned compounds the reaction mixture was extracted with ether, since *m*- and *p*-hydroxybenzaloximes are soluble in water. The ether was removed by a current of dry air, but in each case the original *anti*-oxime was obtained. The solid remaining after the decomposition of the hydrochloride of salicylaloxime with sodium carbonate solution was crystallised from benzene and light

petroleum, and proved to be the original oxime, melting at 57°. The hydrochlorides were also decomposed with dilute ammonia cooled with ice, but no evidence could be obtained of the formation of a *syn*-derivative (compare Luxmoore, T., 1896, **69**, 177). The hydrochlorides of the ortho- and para-compounds were prepared in dry chloroform solution, the meta-compound being insufficiently soluble in this medium for this purpose, but no evidence could be obtained of the formation of a *syn*-derivative (compare Forster and Dunn, T., 1909, **95**, 430). An attempt was also made to effect the transformation by passing dry hydrogen chloride into a solution of the oxime cooled in a freezing mixture of ice and calcium chloride (compare Luxmoore, *loc. cit.*); the hydrochlorides so obtained proved, however, to be identical with those already prepared, and yielded the *anti*-oxime with sodium carbonate solution.\* The hydrochloride of *m*-hydroxybenzaloxime was obtained by Beckmann's method (*Annalen*, 1909, **365**, 261), by heating the aldehyde in alcoholic solution with hydroxylamine hydrochloride for three hours at 50°; the solution was then diluted, treated with sodium carbonate solution, and extracted with ether. After removing the ether, the oxime separated as an oil; this was treated at once with acetic anhydride, and yielded the acetyl derivative and no trace of nitrile. A large number of experiments have been made on the above lines, and in certain cases the oxime separated in an oily condition; when this occurred, rather than risk isomeric change during recrystallisation and purification, the oil was treated with acetic anhydride in the cold, but in no instance was any nitrile formed, the normal acetyl derivative being always obtained. *Anti*-oximes were always obtained, whether the experiments were conducted in diffused daylight or in the dark.

Comstock (*Amer. Chem. J.*, 1897, **19**, 485) describes an additive compound obtained by treating benzantialdoxime with cuprous chloride, which on decomposition with sodium hydroxide and treatment with carbon dioxide yields benzsynaldoxime. Attempts were therefore made to prepare similar derivatives of the hydroxybenzaloximes, but without success.

The action of light on the three hydroxybenzaloximes was also investigated (compare Ciamician and Silber, *Ber.*, 1903, **36**, 4268; Brady and Dunn, T., 1913, **103**, 1623). The oximes, suspended in benzene, were sealed in glass tubes and left for five months in a position where they would obtain a maximum amount of sunlight.

\* The flask in which this operation was carried out was closed with a two-holed cork through which passed an adapter from the hydrogen chloride generator and a calcium chloride tube to prevent moisture from the atmosphere condensing within the flask.

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At the end of that time they were examined, but various fractions proved to be unchanged *anti*-oxime.

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