LXVIII.—*The Isomerism of the Oximes. Part XXXIII. The Oximes of Opianic Acid and of Phthalic Anhydride.*

By OSCAR L. BRADY, LESLIE C. BAKER, RICHARD F. GOLDSTEIN, and SAMUEL HARRIS.

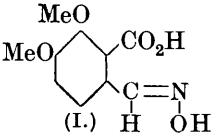
THE oxime of opianic acid (I) was first obtained by W. H. Perkin, jun. (J., 1890, **57**, 1070) by the action of hydroxylamine on an alkaline solution of opianic acid. When, however, hydroxylamine hydrochloride acts upon opianic acid in aqueous alcohol at room temperature, opianic oxime anhydride (II) is produced (Liebermann, *Ber.*, 1886, **19**, 2278, 2923). Both the oxime and its anhydride on fusion are converted into hemipinimide with the evolution of much heat, and the same change occurs when they are heated with solvents containing a trace of acid (Liebermann, *loc. cit.*; Perkin, *loc. cit.*; compare also Liebermann and Stohmann, *Ber.*, 1892, **25**, 89; Roth, *Z. Elektrochem.*, 1910, **16**, 657).

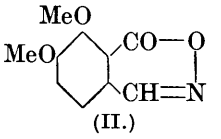
It was thought that further investigation of this change might produce some evidence which would enable a decision to be made between Hantzsch's configurations for the aldoximes and those more recently suggested (Beckmann, Liesche, and Correns, *Ber.*, 1923, **56**, 341; von Auwers and Ottens, *Ber.*, 1924, **57**, 446; Brady and Bishop, J., 1925, **127**, 1357).

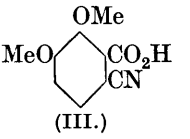
R·CH ‖ HON	R·CH ‖ NOH	R·CH ‖ NOH	R·CH ‖ HON
α-Oxime	β-Oxime	α-Oxime	β-Oxime
Hantzsch		New configurations	

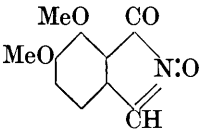
Opianic oxime exists only in one form and behaves in a similar manner to α-aldoximes. The best method of distinguishing between α- and β-aldoximes cannot be applied, since on treatment with acetic anhydride opianic oxime gives, not an acetyl derivative, but opianic oxime anhydride, even when special precautions are taken. However, by the action of 2 : 4-dinitrochlorobenzene on the sodium salt of opianic oxime the dinitrophenyl ether is formed, as is the case with α-benzaldoxime and substituted α-benzaldoximes, whereas β-benzaldoxime gives the aldehyde on treatment with this reagent (Brady and Truszkowski, J., 1924, **125**, 1087). There is, moreover, no reason to suppose that in the formation of opianic oxime there is any exception to the, so far, invariable experience that the action of an alkaline solution of hydroxylamine on an aldehyde in which the aldehyde group is directly attached to the benzene ring produces the α-aldoxime.

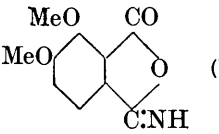
Adopting the new configurations, opianic oxime must, therefore, be represented as (I).


(I.)


(II.)

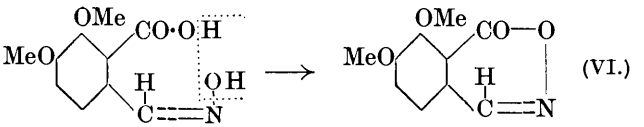

(III.)

(IV.) 

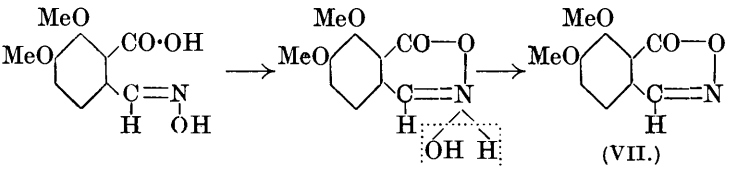

(V.)

Opianic oxime anhydride is best represented by (II). Of other possibilities, (III) has been excluded by the synthesis of this acid by Hoogewerff and van Dorp (*Rec. trav. chim.*, 1895, **14**, 274), (IV) and (V) are unlikely, since the compound is unaffected by boiling acetic anhydride—a reagent which would acetylate (V) and might be expected to convert (IV) into hemipinimide by a Beckmann change (Brady and Dunn, J., 1926, 2411).

Adopting the new configurations, the formation of the anhydride from the oxime may be represented as a simple ring closure between vicinal groups,

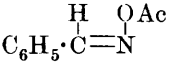
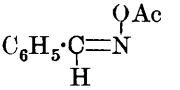

(VI.)

or by a mechanism analogous to that employed by Meisenheimer (*Ber.*, 1924, **57**, 278) to explain the formation of an anhydride from γ-benzildioxime.

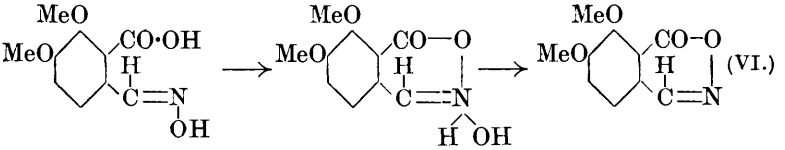

(VII.)

We prefer the second mechanism, because opianic oxime anhydride behaves as the acyl derivative of a β-aldoxime, giving the nitrile (III) and not the original oxime on warming with alkalis. Since opianic oxime is an α-aldoxime, during anhydride formation a change of configuration must have taken place. This occurs only if the second mechanism be adopted, (VI) representing an acyl derivative of an α-aldoxime (compare acetyl-α-benzaldoxime, VIII), and (VII)

an acyl derivative of a β-aldoxime (compare acetyl-β-benzaldoxime, IX).

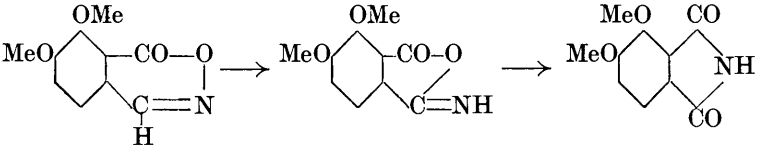
(VIII.)   (IX.)

If Hantzsch's configurations of the aldoximes be adopted, in order that a change of configuration shall take place during anhydride formation, the constitution (VI) must be assigned to the anhydride. Such a structure seems improbable on account of the difficulty of translating it into a spatial formula.

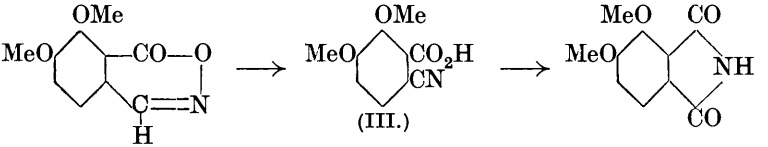


The behaviour of opianic oxime anhydride accordingly supports the new configuration of the aldoximes.

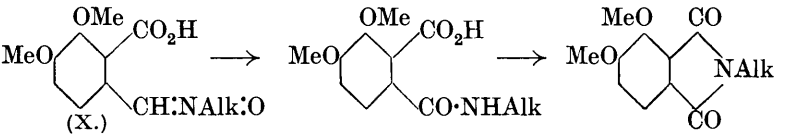
The formation of hemipinimide from opianic oxime anhydride may be regarded as taking place either through a *trans*-Beckmann change,



or through the intermediate formation of 2-cyano-5 : 6-dimethoxybenzoic acid (III), which has been shown to give hemipinimide on heating (Hoogewerff and van Dorp, *loc. cit.*).

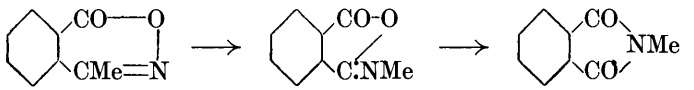


The chief argument in favour of the former is that we have found that the *N*-alkyl derivatives of opianic oxime (X) on fusing, on



heating in solvents in the presence of acids, or on boiling with acetic anhydride, give alkyl hemipinimides. Here there is no possibility

of nitrile formation and the reaction is best interpreted as a Beckmann change (compare also the change of the oxime of lævulic acid to *N*-methylsuccinimide; Bredt and Böddinghaus, *Annalen*, 1889, **251**, 316). On the other hand, in favour of the cyano-acid mechanism the following considerations can be urged. Allendorff (*Ber.*, 1891, **24**, 2347) was able to isolate *o*-cyanobenzoic acid as an intermediate product in the conversion of the analogous phthalaldehydic oxime anhydride into phthalimide by heat. The isolation of the cyano-acid in the case of opianic oxime anhydride could not be expected, for, whereas *o*-cyanobenzoic acid changes to phthalimide at a temperature above the melting and transition point of the oxime anhydride, 2-cyano-5 : 6-dimethoxybenzoic acid changes to hemipinimide at a temperature at which opianic oxime anhydride is stable. Opianic oxime anhydride does not contain a quinquevalent nitrogen atom, the presence of which Brady and Dunn (*loc. cit.*) regard as necessary before the Beckmann change can occur. Finally we have found that the anhydride of the oxime of acetophenone-*o*-carboxylic acid (Gabriel, *Ber.*, 1883, **16**, 1995) is unaltered on melting, can be distilled unchanged under reduced pressure, and is not affected by heating for 10 minutes at 100° with concentrated sulphuric acid. Nitrile formation cannot occur in this case, but a Beckmann change should give *N*-methylphthalimide.



It seems, therefore, that the cyano-acid must be the intermediate stage in the change of opianic oxime anhydride to hemipinimide.

The action of methyl sulphate upon an alkaline solution of opianic oxime or of *O*-methylhydroxylamine upon opianic acid leads to the formation of *O*-methylopianic oxime, a stable compound unchanged on fusion.

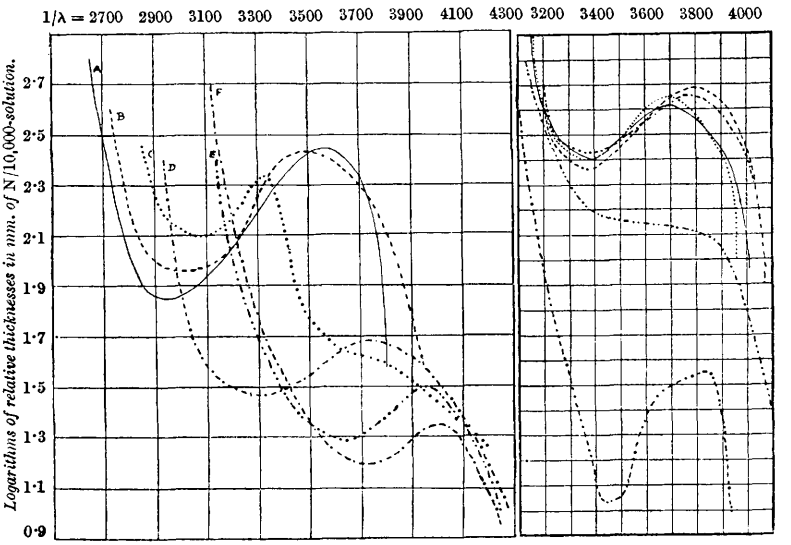
We have measured the absorption spectra of opianic oxime, its anhydride, and *O*- and *N*-methyl ethers and those of hemipinimide and *N*-methylhemipinimide (Fig. 1). The curves for the oxime and the *O*- and *N*-ethers are normal (compare Brady, J., 1914, **105**, 2111), but the curve for the anhydride differs widely from those usually obtained for acylated aldoximes (Brady and Grayson, unpublished work) and suggests a relationship between the anhydride and hemipinimide which is not borne out by their chemical properties. The curves, however, cannot be said to throw much further light on the constitution of the compounds.

In connexion with this work the possibility of an analogous reaction between hydroxylamine and 4-nitrobenzaldehyde-*o*-

sulphonic acid has been investigated, but no indication of the formation of the expected 4-nitrosaccharin was obtained even on heating the aldehyde with aqueous hydroxylamine hydrochloride at 160°.

The two forms, white and yellow, of phthaloxime (Lassar-Cohn, *Annalen*, 1880, **205**, 295; Lach, *Ber.*, 1883, **16**, 1781; Pratt and Orndorff, *Amer. Chem. J.*, 1912, **47**, 89) have been re-investigated.

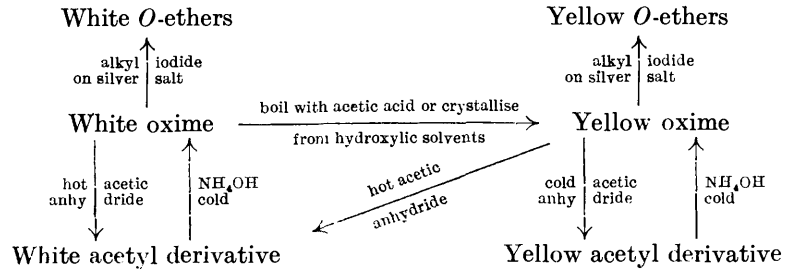
FIG. 1. FIG. 2.



A = *Methylhemipinimide.* B = *Hemipinimide.* C = *Opianic oxime anhydride.* D = N-*Methylopianic oxime.* E = O-*Methylopianic oxime.* F = *Opianic oxime.*

——— *Yellow Phthaloxime.* ..... *White Phthaloxime.* -·-·-·-·- *Yellow* O-*Methylphthaloxime.* - - - - - - *White* O-*Methylphthaloxime.* ·-·-·-·-·- N-*Methylphthaloxime.* ·-·-·-·-·- *Phthalimide.*

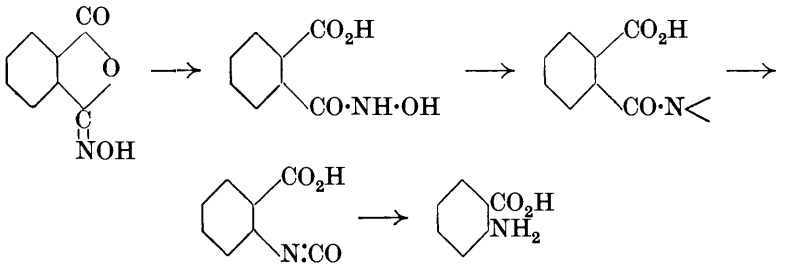
Both forms melt and decompose at the same temperature and both yield series of derivatives in which the characteristic difference in colour persists. The various reactions may be summarised thus:



Analogous derivatives of the white and the yellow oxime always melt at the same temperature and the white and the yellow form show no depression of melting point in admixture. Both oximes give deeply coloured alkali salts, from which the original oximes are reprecipitated by acids. Pratt and Gibbs (*Philippine J. Sci.*, 1913, **8**, 165) measured the absorption spectra of the two phthaloximes and of a number of their derivatives and also those of phthalimide, phthalanil, and related compounds. From their curves, which agree very closely with those obtained by us (Fig. 2), and from the other reactions of the phthaloximes they concluded that these compounds are stereoisomerides. Pratt and Orndorff assumed that the ethers they obtained were both *O*-ethers, and we have now established this in the case of the methyl ethers by the quantitative formation of methyl iodide on boiling them with hydriodic acid and by the production of *O*-methylhydroxylamine by hydrolysis. By methylating a suspension of the sodium salts in methyl alcohol with either methyl iodide or methyl sulphate, only the *O*-ethers were obtained, no *N*-methyl derivative being formed. However, an *N*-methyl compound has been prepared from phthalic anhydride by the action of *N*-methylhydroxylamine ; this compound was white and we were unable to prepare a yellow modification under any conditions. The absorption spectra of the two oximes of the sodium salts and *O*-methyl ethers have been reinvestigated and that of the new *N*-ether has been determined. It was noticed that the derivatives of the yellow phthaloxime fluoresce green when their solutions in absolute alcohol are exposed to light from a tungsten arc, and that the yellow oxime, the white oxime, and its derivatives do not. The close similarity of the absorption spectra and the identity of melting points of the two forms rule out the possibility of one having the hydroxyimide structure $C_6H_4(CO)_2{:}N{\cdot}OH$ and differentiate the compounds from chromoisomerides. Polymorphism is excluded by the differential action of light on solutions of the two forms and by the fact that the solutions of the white or yellow oximes in alkali regenerate the parent compounds on acidification. Whilst it is true that the absorption spectra of the two forms differ by about the same amount as do those of α- and β-aldoximes, there is no evidence otherwise that they are stereoisomerides in the ordinary sense. The stereoisomeric oximes usually differ considerably in melting point and give normal fusion curves when mixed. The phthaloximes, in their chemical reactions, behave identically and, in spite of special attention, no indication has been obtained of those differences in chemical behaviour which distinguish stereoisomerides. We believe, therefore, that the phthaloximes exhibit a special type of

isomerism for which an explanation has still to be found and of which numerous examples are now accumulating (compare the white and the yellow form of diphthalyl-2 : 7-naphthylenediamine, Kuhn, Jacob, and Fürter, *Annalen*, 1927, **455**, 256, and also the work of Heller, *Ber.*, 1925, **58**, 838; 1927, **60**, 909). We believe that the white and the yellow forms of some carbanilino-derivatives of the oximes (Goldschmidt and van Rietschoten, *Ber.*, 1893, **26**, 2089; Brady and Thomas, J., 1922, **121**, 2100) and the white and the yellow form of *iso*nitrosomalonmono-*p*-tolylamide (Plowman and Whiteley, J., 1924, **125**, 590) also exhibit this new type of isomerism, which may perhaps be called xanthoisomerism.

Lassar-Cohn obtained anthranilic acid from the white phthaloxime by the action of one equivalent of boiling alcoholic potassium hydroxide, but was unable to repeat this result. We were likewise unsuccessful under these conditions, but obtained small yields of anthranilic acid from both white and yellow oximes by using a higher temperature and amyl-alcoholic potassium hydroxide. The change is probably an example of the Hofmann reaction :



Experimental.

Action of Acetic Anhydride on Opianic Oxime.—Opianic oxime was prepared by Perkin's method (*loc. cit.*), 30% potassium hydroxide solution being used in place of the dilute alkali recommended by him, since this gives much better results. The oxime dissolved when treated with the minimum amount of acetic anhydride at room temperature, but no acetyl derivative separated on cooling to −20°; opianic oxime anhydride crystallised when the solution was poured into ice-cold water.

Action of 2 : 4-Dinitrochlorobenzene on Opianic Oxime.—The oxime (3 g.) was dissolved in alcohol, and a solution of sodium ethoxide (sodium, 0·7 g., in 12 c.c. of alcohol) added; the disodium salt then separated as a white precipitate. To the cooled suspension, 2 : 4-dinitrochlorobenzene (3 g. in 9 c.c. of hot alcohol) was added, the brown solution obtained was kept for an hour, and the preci-

pitate was then collected and washed first with a little alcohol and then thoroughly with water to remove sodium chloride. On crystallising from alcohol, it gave 2 : 4-*dinitrophenylopianic oxime* as bright yellow needles, m. p. 146° (Found : N, 11·0. $C_{16}H_{13}O_9N_3$ requires N, 10·7%).* Hydrolysis by heating in the water-bath for 5 hours with 6*N*-sodium hydroxide gave sodium dinitrophenoxide, but hemipinic acid could not be isolated from the rather tarry alkaline solution.

Action of Alkalis on Opianic Oxime Anhydride.—To a warm solution of potassium hydroxide (10 g.) in water (50 c.c.), opianic oxime anhydride (2·6 g.) was added with mechanical stirring; it dissolved to a pale yellow solution. In order to detect opianic oxime, methyl sulphate (4 c.c.) was added and the stirring continued for 2½ hours. The solution was cooled in ice and concentrated hydrochloric acid (15 c.c.) added slowly; an oil separated which soon solidified and after drying in a desiccator formed a sandy powder (0·95 g.), m. p. 74—80°, resolidifying immediately to hemipinimide. In all its properties this compound was identical with the 2-cyano-5 : 6-dimethoxybenzoic acid described by Hoogewerff and van Dorp (*loc. cit.*).

When the reaction was carried out at 0°, uncrystallisable sticky solids were obtained from which only hemipinimide could be isolated. No trace of *O*-methylopianic oxime was detected in any experiment.

The anhydride (1 g.) was dissolved in a solution of sodium ethoxide (sodium, 0·23 g., in 20 c.c. of hot alcohol) and 2 : 4-dinitrochlorobenzene (1 g. in 5 c.c. of hot alcohol) added. No 2 : 4-dinitrophenylopianic oxime separated, but after 3 days dinitrophenetole crystallised, this being formed by the action of the alkali and alcohol on the dinitrochlorobenzene.

N-*Methylopianic Oxime.*—A solution of opianic acid (5 g.) in potassium hydroxide (5·5 g. in 50 c.c. of water) was cooled and to it was added a concentrated aqueous solution of *N*-methylhydroxylamine hydrochloride (3 g.). The mixture was kept at room temperature for 12 hours, 2*N*-hydrochloric acid (32 c.c.) was then added, and the precipitate produced was crystallised from dilute alcohol, N-*methylopianic oxime* being obtained as colourless prisms, m. p. 180·5° (decomp.) (Found : N, 5·9. $C_{11}H_{13}O_5N$ requires N, 5·9%).

N-*Methylhemipinimide.*—*N*-Methylopianic oxime (5 g.) was boiled with water (100 c.c.) under reflux for 3 hours. After cooling, a small quantity of *N*-methylhemipinimide slowly crystallised.

* In the determination of nitrogen in opianic acid derivatives by Dumas' method, cuprous chloride must be mixed with the copper oxide to prevent the formation of methane.

The mother-liquor on evaporation to small bulk yielded some crystals of unchanged *N*-methylopianic oxime; these were removed and the filtrate was warmed with 2*N*-sodium hydroxide, methylamine and sodium hemipinate being produced. The main product of the reaction was apparently the soluble methylamine hydrogen salt of hemipinic acid; Liebermann (*loc. cit.*) obtained ammonium hydrogen hemipinate similarly from opianic oxime anhydride. No compound analogous to the anhydride of the oxime was obtained either in this experiment or when opianic acid (6 g.) in alcohol (18 c.c.) was shaken with *N*-methylhydroxylamine hydrochloride (2·9 g.) for 45 minutes (compare Liebermann, *loc. cit.*). The acid dissolved and *N*-methylopianic oxime soon crystallised: the alcoholic solution on evaporation gave only ψ-opianic ester (Anderson, *Annalen*, 1853, **86**, 194).

When *N*-methylopianic oxime was heated for 10 minutes at 180° in an evaporating basin, some ebullition occurred just above the melting point. The intramolecular change, however, proceeded without the violence that characterises the change of opianic oxime to hemipinimide. After cooling, the product was stirred with a little alcohol, and the solid crystallised three times from alcohol, pure *N*-methylhemipinimide being obtained.

Opianic acid (5 g.) and *N*-methylhydroxylamine hydrochloride (1·7 g.) were heated together under reflux for 3 hours with 80% alcohol (30 c.c.). On cooling, a solid separated which gave pure *N*-methylhemipinimide after one crystallisation from alcohol.

Hemipinimide (2·5 g.), prepared by boiling opianic acid in alcoholic solution with hydroxylamine hydrochloride, was dissolved in hot dry amyl alcohol, and a solution of potassium (0·75 g.) in dry amyl alcohol added; after cooling, the solid was collected, washed with dry ether, and quickly transferred to a desiccator containing solid sodium hydroxide. The yield of potassium hemipinimide was almost quantitative (compare Hammick and Locket, J., 1922, **121**, 2362). The salt was heated with excess of methyl iodide for 5 hours in a sealed tube at 150°; the solid obtained gave *N*-methylhemipinimide, m. p. 168°, after two crystallisations from alcohol. Freund and Heim (*Ber.*, 1890, **23**, 2905) obtained this compound by the action of dilute nitric acid on the methylamide of methylhydrastinine.

O-*Methylopianic Oxime*.—Opianic acid (5 g.) was dissolved in 2*N*-sodium hydroxide (30 c.c.), a solution of *O*-methylhydroxylamine hydrochloride (2·2 g. in 25 c.c. of water) added, and the mixture kept in a closed bottle for 12 hours. Addition of dilute hydrochloric acid then precipitated O-*methylopianic oxime*, which crystallised from benzene and light petroleum or from chloroform

in colourless cubes, m. p. 112° (Found : N, 6·3. $C_{11}H_{13}O_5N$ requires N, 5·9%).

Opianic acid (5 g.) was dissolved in 4*N*-potassium hydroxide (100 c.c.), and a concentrated aqueous solution of hydroxylamine hydrochloride (2·5 g.) added slowly. To the cold solution, methyl sulphate (10 g.) was added cautiously with cooling and shaking. The mixture was kept for 2 hours, and a slight excess of dilute hydrochloric acid added; *O*-methylopianic oxime then separated in good yield. It was purified as before.

N-*Benzylopianic Oxime.*—This was prepared from opianic acid and *N*-benzylhydroxylamine hydrochloride in exactly the same way as *N*-methylopianic oxime (compare Scheiber, *Ber.*, 1911, **44**, 762). On heating it for 6 hours in alcoholic solution with a trace of hydrochloric acid, *N*-benzylhemipinimide (van der Meulen, *Rec. trav. chim.*, 1896, **15**, 282) was obtained. This compound was also formed by heating opianic acid with *N*-benzylhydroxylamine hydrochloride in alcoholic solution.

Methylation of the Sodium Salts of the Phthaloximes.—The white and the yellow methyl ether described by Pratt and Orndorff were prepared by their method from the corresponding silver salts of the oximes. These authors experienced difficulty in alkylating the sodium salts, but we have been successful with both methyl iodide and methyl sulphate; care, however, must be taken to avoid excess of alkali, which readily decomposes the oximes to hydroxylamine and phthalic acid.

The yellow phthaloxime (2·50 g.) was dissolved in the minimum amount of methyl alcohol, and the red sodium salt precipitated by the addition of sodium methoxide (sodium, 0·35 g., in methyl alcohol). Methyl iodide (2·5 c.c.) was added to the suspension, and the mixture kept in a closed flask for 5 days; the red sodium salt had then disappeared and the liquid was clear orange-yellow. The solution was evaporated at room temperature, and the residue extracted with boiling light petroleum; on cooling, crystals of the yellow *O*-methyl ether of phthaloxime were obtained identical with those obtained from the silver salt (Found : OMe, 17·4. Calc. : OMe, 17·5%). Similarly, from the white phthaloxime the white *O*-methyl ether of phthaloxime was obtained identical with that prepared from the silver salt (Found : OMe, 17·3%).

A solution of white phthaloxime (5·02 g.) in methyl alcohol (75 c.c.) was treated with sodium methoxide (0·71 g. of sodium in the minimum amount of methyl alcohol), and methyl sulphate (5·6 c.c.) added. The mixture was kept for 1¾ hours with occasional shaking, the reaction then being complete. After 45 c.c. of the solvent had been removed in a vacuum, and the remainder cooled, a mixture of the

white *O*-methyl ether and sodium sulphate separated, from which the ether was extracted with chloroform; the filtrate on concentration yielded more *O*-ether. Similarly, the yellow oxime gave the yellow *O*-ether. In all these methylations the addition of a little water greatly increases the reaction velocity without, however, much affecting the yield, which was never more than 25%. Although a careful search was made, in no case was any trace of an *N*-methyl derivative detected.

Hydrolysis of O-*Methylphthaloxime.*—White *O*-methylphthaloxime (9·8 g.), dissolved in 2*N*-sodium hydroxide (80 c.c.), was heated on the water-bath for an hour and the solution was then acidified with hydrochloric acid and cooled. The precipitated phthalic acid was removed, and the solution evaporated to dryness on the water-bath. The residue was washed with ether to remove phthalic acid and extracted twice with small quantities of hot absolute alcohol; on cooling, and addition of ether to the combined extracts, *O*-methylhydroxylamine hydrochloride (m. p. 149—151°) was precipitated. It was further identified by conversion into α-*O*-methyl-*m*-nitrobenzaldoxime.

N-*Methylphthaloxime.*—A solution of *N*-methylhydroxylamine hydrochloride (9 g. in 9 c.c. of water) and sodium carbonate (5·7 g. in 160 c.c. of water) was heated to 60°, finely powdered phthalic anhydride (12·7 g.) slowly stirred in, and the solution kept at 60° for 1¼ hours. A white, crystalline precipitate separated which after crystallisation from alcohol gave N-*methylphthaloxime* as colourless crystals, m. p. 121—122° (Found: N, 7·9. $C_9H_7O_3N$ requires N, 7·9%). This compound, on boiling for a short time with hydrochloric acid, gave phthalic acid and *N*-methylhydroxylamine. Boiling with concentrated hydriodic acid gave methylamine, which was identified by Valton's method (J., 1925, **127**, 40). Variations in the experimental procedure failed to yield a yellow form.

Action of Potassium Hydroxide on the Phthaloximes.—White or yellow phthaloxime (5·4 g.) in amyl alcohol (180 c.c.) was treated with one equivalent of potassium hydroxide (1·86 g.) in water (12 c.c.), and the mixture boiled under reflux for 2 hours; the red colour of the potassium salt had then changed to clear yellow. Most of the solvent was removed in a vacuum, and the solid, which separated on cooling, was collected and dissolved in the minimum amount of hot water; on just acidifying the solution with acetic acid and cooling, anthranilic acid separated; it was obtained pure after one crystallisation from hot water.

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