JOURNAL

OF

THE CHEMICAL SOCIETY.

PAPERS READ BEFORE THE CHEMICAL SOCIETY.

I.—*Some Derivatives of Pr 1n-Methylindole.*

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Introduction.

IN his classic researches on the compounds of the indigo-group, Baeyer obtained, by the reduction of isatin, successively—

Dioxindole, $\text{C}_6\text{H}_4\langle\begin{smallmatrix}\text{CH}(\text{OH}) \\ \text{—NH—} \end{smallmatrix}\rangle\text{CO}$; Oxindole, $\text{C}_6\text{H}_4\langle\begin{smallmatrix}\text{CH}_2 \\ \text{NH} \end{smallmatrix}\rangle\text{CO}$;

and Indole, $\text{C}_6\text{H}_4\langle\begin{smallmatrix}\text{CH} \\ \text{NH} \end{smallmatrix}\rangle\text{CH}$.

Up to the present time, the methyl-derivatives of these compounds have been but little studied, and it seemed probable that they might be obtained from Pr 1n-methylindole (for nomenclature, see E. Fischer, *Annalen*, **236**, 116), which, thanks to the researches of E. Fischer and O. Hess (*Ber.*, **17**, 559), can now be prepared in quantity without difficulty.

Fischer and Hess (*ibid.*, p. 561) have shown that methylindole can be converted into methylpseudoisatin by a very remarkable reaction. They found that when methylindole or methylindolecarboxylic acid is treated with a solution of sodium hypochlorite, a crystalline precipitate is formed, which on boiling with alcoholic potash yields methylpseudoisatin.

The intermediate product was analysed by Fischer and Hess, but the analysis was insufficient to decide whether the substance had the formula $\text{C}_9\text{H}_5\text{NBr}_2\text{O}$ or $\text{C}_9\text{H}_7\text{NBr}_2\text{O}$. At Professor Emil Fischer's

suggestion, I have made a detailed examination of the reaction, the results of which are given in the following paper.

The product of the action of sodium hypochlorite on methylindole or methylindolecarboxylic acid has the formula $C_8H_7NBr_2O$, and is most probably a dibromo-derivative of methyloxindole, having the formula $C_8H_4<\overset{-CBr_2}{N(CH_3)}>CO$, since with phenylhydrazine it gives a crystalline derivative, which is identical with methylpseudoisatin-phenylhydrazone. The latter must have the constitution

as phenylhydrazine never reacts with a carbonyl-group which is directly combined with nitrogen (see Baeyer, *Ber.*, **16**, 2188). From this it follows that the two bromine-atoms must be in the Pr 3-position as given in the above formula.

This formula also easily explains the formation of methylpseudoisatin when the substance is boiled with alkali or even with water, the two bromine-atoms being displaced by one of oxygen.

By the action of sodium hypochlorite on methylindolecarboxylic acid, the corresponding dichloromethyloxindole is obtained, which corresponds in all its reactions to dibromomethyloxindole.

This peculiar reaction with hypochlorites and hypobromites seems confined to those indoles in which the alkyl-group is attached to the nitrogen-atom. If indole is treated in the corresponding manner, the products of the reaction are not nearly so simple.

Methylpseudoisatinoxime, $C_8H_4<\overset{C(:N\cdot OH)}{N(CH_3)}>CO$, can be obtained in two ways, viz., by the action of hydroxylamine on methylpseudoisatin, or by passing nitrogen trioxide into a solution of methyloxindole.

On reduction in acid solution, dibromomethyloxindole loses first one atom of bromine, forming monobromomethyloxindole,

which by long-continued reduction loses the second atom of bromine, and is converted into methyloxindole, $C_8H_4<\overset{-CH_2}{N\cdot CH_3}>CO$.

By the reduction of methylpseudoisatin in either acid or alkaline solution, methyldioxindole, $C_8H_4<\overset{CH(OH)}{N(CH_3)}>CO$, is obtained.

Experimental Part.

The methylindolecarboxylic acid necessary for this work was prepared according to the directions of Fischer and Hess (*Ber.*, **17**, 561),

by warming methylphenylhydrazone-pyroracemic acid with dilute hydrochloric acid. The crude acid thus obtained is sufficiently pure for further experiments.

The pyroracemic acid required was prepared by Döbner's method (*Annalen*, **242**, 268), which gives a very satisfactory yield of the pure acid.

The action of sodium hydrobromite on methylindolecarboxylic acid was found to proceed best under the following conditions :—

5 grams of the crude acid are dissolved in dilute caustic soda solution, and boiled with animal charcoal for a few minutes. The filtered liquid is gradually added to a well-cooled mixture of 22.5 grams of bromine in about 900 c.c. of water, to which sufficient caustic soda had been added to neutralise the bromine, and the whole continually shaken during the addition. The substance separates at once in fine needles, the colour of which, in the various experiments, varied from light brown to dark red.

In order to purify the substance, the crystals are collected, well washed with water, dissolved in alcohol and boiled with animal charcoal. The filtered solution is then partially evaporated, and on cooling small yellow tables crystallise out. These are separated from the mother-liquor on the filter-pump, twice recrystallised from alcohol, and finally dried over sulphuric acid in a vacuum.

By this means the substance is obtained in almost white tables, which melt with decomposition at 204°. On analysis, numbers were obtained,* which agree well with the formula $\text{C}_6\text{H}_7\text{NBr}_2\text{O}$.

A comparison of this formula with that of methylindole shows that it differs from the latter in that it contains two atoms of hydrogen less, and the elements Br_2O more. As it is easily converted into methylpseudoisatin, the bromine substitution must have taken place in the pyrroline-ring. In order to determine whether these bromine-atoms are attached to the *same* or to *different* carbon-atoms, the substance was subjected to the action of phenylhydrazine.

For this purpose, 4 grams of the crude product were dissolved in warm alcohol, and added to a solution of 5 grams of phenylhydrazine hydrochloride, and 7.5 grams of sodium acetate dissolved in as little water as possible. In a short time, the liquid became dark brown, and on addition of water the product of the reaction was completely precipitated as a yellow oil, which crystallised on standing. The crystals were collected, washed, and twice recrystallised from benzene.

* For analytical numbers, &c., in this and the remaining analyses, see *Annalen*, **248**, 114 &c.

It forms fascicular groups of small yellow needles which melt at 144—145° (uncorr.), and gave on analysis numbers agreeing with those required for methylpseudoisatin-phenylhydrazone. A comparison of its properties with the compound obtained from methylpseudoisatin and phenylhydrazine showed conclusively that the two substances were identical.

From this it follows that the two bromine-atoms are attached to the same carbon-atom in the pyrroline-ring, which condition is fulfilled only by the two following formulæ:—

The first would be dibromomethyloxindole, and the second dibromomethylpseudoindoxyl.

The hydrazones of the compound under discussion and of methylpseudoisatin being identical, the two bromine-atoms in the one must correspond with that carbonyl-group in the other which is acted on by phenylhydrazine. Now, it is well known that phenylhydrazine never acts on a carbonyl-group which is directly connected with nitrogen, so that in methylpseudoisatin the carbonyl-group in the Pr 3-position must be the one attacked, and the hydrazone formed must have the formula $\text{C}_6\text{H}_4 < \overset{\text{C}(\text{N} \cdot \text{NH} \cdot \text{C}_6\text{H}_5)}{\underset{\text{N}(\text{CH}_3)}{\text{---}}} > \text{CO}$. It follows, therefore, that in the brominated compound the two bromine-atoms must also occupy the Pr 3-position, as given in the first of the above formulæ.

The substance consequently is dibromomethyloxindole. Its chief properties are as follows:—

It crystallises from alcohol in yellowish-white tables, which, when quickly heated, melt with decomposition at 204°. If heated slowly, however, it becomes brown at 170°, and melts at 180°. It is readily soluble in alcohol, ether, chloroform, and benzene, but only sparingly in light petroleum, and insoluble in cold water. On boiling with water, it is converted into methylpseudoisatin. It reacts very readily with alkalis, ammonia, amines, hydrazines, and reducing agents. If shaken with benzene containing thiophen and strong sulphuric acid, a brown coloration is produced, which, however, after standing for several hours, becomes changed to the same blue as that produced by methylpseudoisatin.

The preparation of this substance corresponds exactly with that of dibromomethyloxindole. The solution of methylindolecarboxylic acid in alkali is purified by boiling with animal charcoal, and

gradually added to a cold dilute solution of sodium hypochlorite, care being taken that the latter is in excess. The substance separates first in small oily drops, which soon solidify to small brownish-white needles. These are collected, well washed, and recrystallised several times from alcohol or acetone. Thus purified it forms white needles which melt at 145—147°. The numbers obtained on analysis agree well with those required by the formula $C_9H_7NCl_2O$.

Dichloromethyloxindole dissolves much more readily in alcohol than the corresponding bromine-compound, and is also easily soluble in acetone and ether, but insoluble in water. Towards reagents it behaves in exactly the same manner as dibromomethyloxindole, but it is not so easily decomposed by heat, for, whereas the former begins to decompose at 170°, the latter can be heated to 210° without any change taking place.

This compound was obtained by Fischer and Hess (*loc. cit.*) from dibromomethyloxindole by boiling it with alcoholic potash. Instead of this, it was found more advantageous to boil the bromine-compound with water. About 8 grams of crude dibromomethyloxindole are suspended in 300 grams water, and the whole boiled for two or three hours, using a reflux condenser. The solution becomes deep red, and a considerable quantity of resinous matter separates. This is filtered off, and the clear solution concentrated on the water-bath, when beautiful red needles separate on cooling; these, after another crystallisation from water, are quite pure.

The properties of methylpseudoisatin have already been given by Fischer and Hess (*Ber.*, **17**, 561).

To prepare this substance, 1 gram of methylpseudoisatin is dissolved in hot water, and to this an aqueous solution of 1 gram of phenylhydrazine hydrochloride and 1.5 grams of sodium acetate is added. The solution becomes turbid almost immediately, and after a short time oily drops separate which crystallise on cooling. The crystals are collected, washed, recrystallised from alcohol or benzene, and dried at 100°. The results of its analysis are in full agreement with the above formula.

Methylpseudoisatinphenylhydrazone crystallises in fascicular groups of small, yellow needles, which melt without decomposition at 145—146°. It is easily soluble in alcohol and benzene, sparingly in ether, and insoluble in water and light petroleum.

As has already been stated, the product obtained by the action of phenylhydrazine on dibromomethyloxindole is identical with this hydrazone.

The preparation of this oxime is best carried out as follows :—

Aqueous solutions of methylpseudoisatin and hydroxylamine sulphate are mixed, and allowed to stand. The liquid soon becomes turbid, and in about 12 hours the reaction is complete, part of the oxime separating as a bulky amorphous precipitate, while part remains in solution.

In order to isolate the oxime, the whole is shaken with ether 10 times successively, the ethereal solution dried with calcium chloride, the ether distilled off, and the residue, which is a yellow, crystalline mass, purified by recrystallisation from hot water.

In this manner the oxime is obtained as a light yellow substance crystallising in small needles, which on heating become plastic at 170°, and melt at 180—183°. Even after repeated crystallisation from acetone, the melting point does not become constant. The corresponding ethylpseudoisatinoxime was found by Baeyer (*Ber.*, **16**, 2196) to behave in a similar manner.

Methylpseudoisatinoxime is fairly soluble in hot, but much less in cold water, easily in alcohol, acetone, ether, and benzene.

Reduction of Dibromomethyloxindole in Acid Solution.

Dibromomethyloxindole is very easily acted on by reducing agents, especially in acid solution. The reduction proceeds best as follows :—

To a mixture of dibromomethyloxindole with an excess of zinc-dust, suspended in alcohol, concentrated hydrochloric acid is gradually added in small portions, the whole being shaken after each addition. After a few minutes, the dibromomethyloxindole dissolves, forming a clear yellow solution, which is warmed for a short time on the water-bath. After the solution has been filtered from the unaltered zinc-dust, it is largely diluted with water, and heated on the water-bath till the alcohol is completely evaporated. The products of the reaction then separate for the most part as reddish-brown oily drops, which collect at the bottom of the dish. The clear, colourless mother-liquor is poured off, and treated as shown later on.

The oil is now boiled with a large quantity of water for some time, and thereupon partially dissolves. The liquid is filtered hot and from the colourless solution white needles separate on cooling. These are

filtered off, and the mother-liquor utilised for again extracting the residual oil. This process is repeated until the solution no longer yields crystals on cooling. To this solution the colourless mother-liquor above mentioned is added.

The crystalline product was first examined, with the following result:—

After a single recrystallisation from acetone, the substance was obtained in white, lustrous plates melting at 132—134°. It gave, on analysis, numbers which agree well with the formula $\text{C}_9\text{H}_8\text{NBrO}$, and is, therefore, as one would expect, monobromomethyloxindole.

It is soluble to some extent in hot water, scarcely at all in cold. It dissolves easily in alcohol, ether, and acetone, and crystallises best from the latter.

The bromine in this compound is very firmly combined. On boiling with caustic potash solution, it dissolves, but crystallises out unaltered on cooling.

The mother-liquor was then examined, being treated as follows:—

The solution is extracted 10 times with ether, the ethereal solution dried over calcium chloride, and the ether evaporated. The residue is an oil, which on standing for a short time solidifies to a beautiful, radiating, crystalline mass.

If this mass be now crystallised from water it is obtained in white, transparent needles, some of which are 4—5 cm. long. These, however, still contain 2—3 per cent. of the monobromo-derivative. To completely eliminate the bromine, the substance must be dissolved in hot water, and boiled for half an hour with zinc-dust and hydrochloric acid. This powerful reducing action has, however, also the effect of causing a considerable diminution in the yield.

The solution, after filtering off the zinc-dust, is extracted with ether as before, and the residual oil recrystallised from water. It is thus obtained in small, white needles, which, for analysis, were dried over sulphuric acid in a vacuum. The numbers obtained on analysis confirmed the supposition that the substance is methyloxindole. It melts at 86—88°, and volatilises slightly with steam. Heated by itself it distils with partial decomposition and formation of a reddish-brown substance. It is fairly soluble in hot water, but much less so in cold water and in light petroleum, easily in alcohol, ether,

acetone, and benzene. It is precipitated from its ethereal solution by light petroleum in fine oily drops, which solidify in a short time, forming beautiful transparent needles.

It does not combine with phenylhydrazine even on long-continued warming. This fact bears out the supposition that in dibromomethyloxindole the bromine-atoms are in the Pr 3-position.

When boiled with caustic potash solution, it does not take up the elements of water, so as to form the corresponding acid,

It dissolves in the hot liquid, but is precipitated unaltered on cooling.

If bromine-water is added to an aqueous solution of methyloxindole, a crystalline precipitate is at once formed. This, however, is not identical either with dibromomethyloxindole or with monobromomethyloxindole, for it is quite insoluble in water and is not acted on by caustic potash solution. It seems probable, therefore, that the bromine is contained in the aromatic nucleus.

By the action of nitrogen trioxide on methyloxindole in dilute aqueous solution, a compound is formed which was found to be identical with methylpseudoisatinoxime. When prepared by this method, however, it is much more difficult to purify.

This compound is obtained by the reduction of methylpseudoisatin. The following method gives the best results:—

4 grams of dibromomethyloxindole are boiled with water for 2 to 3 hours. To the solution thus formed, which contains methylpseudoisatin and hydrobromic acid, zinc-dust is added, and the whole boiled till the liquid is colourless, more acid being added if necessary. The filtered and cooled solution is then extracted 20 times with ether. The residue left on evaporating the ether is always slightly yellow, part of the methyldioxindole being oxidised by the oxygen of the air to methylpseudoisatin.

This is twice recrystallised from benzene, and is thus obtained in the form of colourless needles or prisms. It must be dried over sulphuric acid in a vacuum, as it becomes slightly brown when heated for any length of time at 100°. Its analysis agrees well with the formula $\text{C}_9\text{H}_9\text{NO}_2$. It melts at 149–151° and decomposes on further heating. It is sparingly soluble in cold water, alcohol, ether, and benzene, but easily in the hot liquids. From water and alcohol, the

crystals are always yellowish, but it can, as above stated, be obtained white from its solution in benzene.

If the solution of methyldioxindole is allowed to stand in the air it is gradually oxidised to methylpseudoisatin, but if it be made alkaline oxidation will proceed very rapidly.

One important difference is to be noted in the behaviour of isatin and methylpseudoisatin towards reducing agents. Isatin on reduction in alkaline solution yields isatyd, a compound containing a molecule twice as large as isatin, whereas methylpseudoisatin yields the same product as in acid solution, viz., methyldioxindole.

The following table shows the derivatives of methylindole obtained up to the present time, together with the corresponding indole-compounds.

Indole, m. p. 52°; b. p. 245°.	Methylindole, b. p. 239°.
Oxindole, m. p. 120°.	Methyloxindole, m. p. 86—88°.
Bromoxindole (constitution unknown), m. p. 176°.	Bromomethyloxindole, m. p. 132—134°.
—	Dibromomethyloxindole, m. p. 204°.
—	Dichloromethyloxindole, m. p. 145—147°.
Dioxindole, m. p. 180°.	Methyldioxindole, m. p. 149—151°.
Isatin, m. p. 200—201°.	Methylpseudoisatin, m. p. 134°.
Isatinphenylhydrazone, m. p. 210°.	Methylpseudoisatinphenylhydrazone, m. p. 145—146°.
Isatinoxime, m. p. 202°.	Methylpseudoisatinoxime, m. p. 180—183°.

The above research was carried out in Professor Emil Fischer's laboratory at Würzburg, and I take this opportunity of expressing my best thanks to Professor Fischer for the kind advice and assistance given me throughout the investigation.