To the group of pyrrole syntheses in which the pyrrole ring is closed in the β γ position, belongs the theoretically important method of Piloty and Robinson, from the azines of enolisable ketones (Piloty, *Ber.* (1910), 43, 497; Robinson and Robinson, *Journ. Chem. Soc.* (1918), 113, 639); but the most important is the very general synthesis due to Knorr (*Ber.* (1884), 17, 1638; *Annalen* (1886), 236, 317). Knorr originally reduced isonitroso ketones in the presence of acetoacetic ester with zinc and acetic acid, the isonitroso compound being reduced first to an α-amino ketone, which at once condensed with the keto-ester to give an aminocrotonic ester. This then lost water with formation of a pyrrole.

Further careful investigation of the reaction by Knorr and Lange (*Ber.* (1902), 35, 2998-3008) showed that
better yields of pyrrole could be obtained when the amino ketone was separately prepared and then condensed with a β-keto-ester or β-diketone.

Knorr's synthesis has been widely applied, notably in the synthesis of various hæmopyrroles. However, its extension to the preparation of ring compounds of the hydrogenated indole or carbazole types has been confined almost entirely to one or two examples. Piloty showed that succinyl succinic ester could be condensed with aminoacetone to dimethylidihydropyrindole (I) (Ber. (1910), 43, 489); whilst Duden has shown that α-aminocamphor can be condensed with acetylacetone to the indole derivative (II) (Annalen (1900), 313, 25; Ber. (1901), 34, 3054).

In the present work some exploration of the possibility of extending the Knorr synthesis generally to the preparation of compounds of the hydrogenated indole, carbazole and related types has been made by certain preliminary experiments. In the first of these the open chain β-keto ester or β-diketone of Knorr has been replaced by a cyclic β-diketone—dimethylidihydroresorcinol. After repeated trials it has been found possible to isolate small yields of pyrroles from the reaction mixtures obtained by reducing isonitrosoketones with zinc dust in acetic acid solution in presence of dimethyl dihydroresorcinol. Thus, reduction of isonitrosoacetone in presence of dimethyl-dihydroresorcinol led to formation in 10% yield of 3:6:6-trimethyl-4-keto-
Finally, an experiment was carried out in which 2-isonitroso-l-hydrindone was reduced with zinc dust in acetic acid solution in presence of dimethyldihydro-resorcinol. Although a small yield (about 1%) of a crystalline substance was isolated it was not possible to purify and characterise it.

The fact that condensation of preformed a-amino-ketones with /β-keto esters and /β-diketones always gives better yields of pyrroles than the method in which an a-isonitroso ketone is reduced in presence of the /β-keto ester or /β-diketone, suggests that improved yields of pyrroles may be obtained in the above condensations, and it is proposed to carry out further experiments using the former method.

To a solution of a-isonitroso-a-benzyl acetone (10 g.; cf. Sonn, Ber. (1907), 40, 1666) and acetyl acetone (7 g.) in acetic acid (120 g.) was gradually added zinc dust (30 g.) with good cooling, after which the mixture was allowed to stand for thirty minutes and later was heated to 100° for thirty minutes. It was then filtered whilst hot and the filtrate collected in cold water. A white flocculent precipitate separated which was collected and recrystallised from methyl alcohol. There were thus obtained transparent prisms having a very pink tinge, melting at 165-166°, and

\[ \text{III} \quad \text{IV} \]

In the same way reduction of a-isonitroso-a-benzyl acetone with zinc dust in acetic acid solution in presence of dimethyldihydroresorcinol led to the formation of 3:6:6-trimethyl-2-benzyl-4-keto-4:5:6:7-tetrahydro indole (V), the yield in this instance being 22%. It was previously found by one or two experiments—described in the experimental section—that a-isonitroso-a-benzyl acetone is specially suitable for the formation of pyrroles in the Knorr synthesis.

Attempts to prepare pyrroles by reducing a-isonitroso ketones with zinc dust and acetic acid in presence of 1:3-diketohydrindene proved abortive. Condensation appeared to occur readily enough but no definite pure substances could be isolated from the reaction mixtures.

In a second set of experiments the open chain a-isonitroso ketone of Knorr was replaced by a cyclic a-isonitroso ketone—2-isonitroso-1-hydrindone. It was found possible by reducing 2-isonitroso-1-hydrindone with zinc dust in acetic acid solution in presence of acetyl acetone to isolate a small yield of 2-methyl-3-acetyl-4:5-indeno (1:2)-pyrrole (VI); but the corresponding condensation of 2-isonitroso-1-hydrindone with acetoacetic ester could not be satisfactorily achieved.
Finally, an experiment was carried out in which 2-isonitroso-1-hydrindone was reduced with zinc dust in acetic acid solution in presence of dimethylhydroresorcinol. Although a small yield (about 1%) of a crystalline substance was isolated it was not possible to purify and characterise it.

The fact that condensation of preformed \( \alpha \)-amino-ketones with \( \beta \)-keto esters and \( \beta \)-diketones always gives better yields of pyrroles than the method in which an \( \alpha \)-isonitroso ketone is reduced in presence of the \( \beta \)-keto ester or \( \beta \)-diketone, suggests that improved yields of pyrroles may be obtained in the above condensations, and it is proposed to carry out further experiments using the former method.

Experimental.

2:4-Dimethyl-3-acetyl-5-benzyl pyrrole.

To a solution of \( \alpha \)-isonitroso-\( \alpha \)-benzyl acetone (10 g.; cf. Sonn, *Ber.* (1907), 40, 4666) and acetyl acetone (7 g.) in acetic acid (120 g.) was gradually added zinc dust (30 g.) with good cooling, after which the mixture was allowed to stand for thirty minutes and later was heated to 100° for thirty minutes. It was then filtered whilst hot and the filtrate collected in cold water. A white flocculent precipitate separated which was collected and recrystallised from methyl alcohol. There were thus obtained transparent prisms having a very pink tinge, melting at 165-166°, and
readily soluble in methyl alcohol, ethyl alcohol, ethyl acetate, acetic acid and acetone.

Found C = 79·5, H = 7·5%; calculated for C_{15}H_{17}ON, C = 79·3, H = 7·6%.

A dilute alcoholic solution of this pyrrole when treated with p-dimethylaminobenzaldehyde and hydrochloric acid at once develops a beautiful red colour (Ehrlich’s reaction).

Ethyl-2:4-dimethyl-5-benzyl-pyrrole-3-carboxylate.

Zinc dust (60 g.) was gradually added with constant stirring to a solution of α-isonitroso-α-benzyl acetone (20 g.) and ethyl acetoacetate (15 g.) in glacial acetic acid (220 g.), the temperature not being allowed to rise above 10°. Thirty minutes after completion of the addition the mixture was heated to 90-100° for a further thirty minutes, after which it was filtered and the filtrate poured into cold water. The white solid which separated (12 g.) was collected and recrystallised from methyl alcohol. It was thus readily obtained in large crystals with quite a pronounced pink tinge, melting at 119°.

Found C = 74·6, H = 7·3%; calculated for C_{16}H_{10}O_{2}N, C = 74·7, H = 7·4%.

This pyrrole ester is readily soluble in the usual organic solvents but insoluble in water. In Ehrlich’s pyrrole test it gives an immediate definite rose-red coloration.


Zinc dust (30 g.) was gradually stirred into a solution of α-isonitroso-α-benzyl acetone (12 g.) and dimethyl dihydroresorcinol (11 g.) in glacial acetic acid (120 g.), the temperature being kept below 20°. The solution gradually assumed a green colour during the addition of the zinc (one hour). The mixture was then heated at 90-100° for two hours and was then allowed to stand for 48 hours, after which it was filtered and the filtrate
carefully stirred into cold water. The resulting liquid was allowed to stand at 0° for 24 hours, when a yellow flocculent precipitate (5 g.; 22% of theory) had separated. Recrystallised from ethyl acetate it was obtained in faintly yellow micaceous flakes melting at 197°.

Found C = 80·4, H = 8·0%; calculated for C₁₈H₂₁ON, C = 80·9, H = 7·9%.

The substance was readily soluble in the usual organic solvents but may be recrystallised from alcohol or ethyl acetate. It does not give Ehrlich's reaction for pyrroles, and does not give any colour with ferric chloride in alcoholic solution.


Zinc dust (30 g.) was gradually stirred into a solution of isonitrosoacetone (8 g.) and dimethyldihydroresorcinol (13 g.) in glacial acetic acid (120 g.), the temperature being maintained below 5° throughout the addition. After standing thirty minutes the mixture was finally warmed for thirty minutes and then filtered. Dilution of the filtrate with cold water led to gradual separation of a small amount of the expected pyrrole derivative (2 g.). It was recrystallised with difficulty from ethyl alcohol and thus obtained in small brownish coloured needles, melting at 156°.

Found C = 74·1, H = 8·6%; calculated for C₁₁H₁₅ON, C = 74·6, H = 8·5%.

Very soluble in all the usual organic solvents, this substance gives a very definite rose-red coloration in alcoholic solution when treated with Ehrlich's reagent.


Zinc dust (30 g.) was gradually stirred into a solution of α-isonitroso-α-methyl acetone (10 g.) and dimethyldihydroresorcinol (12·8 g.) in glacial acetic acid (100 g.), the temperature being kept below 10°. Finally, after
standing 30 minutes, and heating at 90-100°, for a further hour the liquid was filtered and the filtrate poured into cold water. Yellow crystals commenced to separate, and after standing overnight at 0° these were collected and recrystallised from ethyl acetate, long yellow needles melting at 228° being thus obtained.

Found C = 75-4, H = 8·9%; calculated for C_{12}H_{17}ON, C = 75·9, H = 9·0%.

From the ethyl acetate mother liquors it was possible to isolate in small quantity a product crystallising in colourless prisms and melting at 173-178°. Owing to the small amount present it was not possible rigidly to purify it. An analysis showed C = 66·0%, H = 8·4%. It seems most probable that this substance is similar to the intermediate described by Knorr (Ber. (1902), 35, 2998-3008) and should have the structure (VII).

\[
\begin{align*}
\text{VII} \\

\end{align*}
\]

In such a substance (C_{12}H_{16}O_{2}N) there would be C = 68·9%, and H = 9·0%.

The 2:3:6:6-tetramethyl-4-keto-4:5:6:7-tetrahydroindole above described is readily soluble in the usual organic solvents, and does not give a red coloration when treated with Ehrlich's reagent in alcoholic solution.

2-Methyl-3-acetyl-4:5-indeno (1:2)-pyrrole (VI).

Zinc dust (20 g.) was gradually stirred into a solution of isonitroso-α-hydrindone (10 g.) and acetyl acetone (9 g.) in acetic acid (80 g.), the temperature being
prevented from rising by cooling the mixture in ice-water. Immediately after the first addition of zinc dust
the solution became bright red in colour—an effect due
to the action of zinc and acetic acid on isonitroso-α-
hydrindone as it occurred even in absence of acetyl
acetone. When excess of zinc had been added the colour
gradually disappeared. After warming for 10 minutes
on the water bath the mixture was filtered and the filtrate
diluted with water. A brown sticky solid separated.
Ether was added and the mixture well shaken. After
allowing the liquids to separate it was observed that
a solid mass had collected at the junction of the two
liquids. It was filtered off and recrystallised from much
alcohol and thus obtained in very small faintly pink
needles melting at 254°.

Found C = 79·1, H = 6·4%; calculated for C₁₄H₁₃ON,
C = 79·6, H = 6·2%.

This pyrrole derivative is but sparingly soluble in the
usual organic solvents but can be recrystallised from
much alcohol. It does not give Ehrlich's test for
pyrroles.

Additional experiments in which isonitroso acetone,
diacetyl monoxime and α-isonitroso-α-benzyl acetone were
reduced with zinc dust in acetic acid solution in presence
of 1:3-diketohydrindene led only to formation of pasty
masses from which no crystalline material could be
isolated.

In other experiments isonitroso-α-hydrindone (10 g.)
was reduced by addition of zinc dust (25 g.) to its
solution in acetic acid (80 cc.) in presence of ethyl
acetoacetate (9 g.). It was found possible by the
procedure described previously to isolate small amounts
of a brownish-red crystalline substance which melted at
195-197°, but was difficult to purify. An analysis showed C = 84·1, H = 6·4%, but these figures are out of agreement for the expected pyrrole.

Finally, in an experiment in which 2-isonitroso-1-hydrindone (6 g.), and dimethyldihydroresorcinol (6) were dissolved in acetic acid (110 cc.) and zinc dust (25 g.) carefully added with cooling, the mixture being finally filtered into water, it was possible to isolate about 1% of a high melting brownish crystalline substance which could be recrystallised from ethyl acetate. The amount was, however, too small to continue further.

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