PYRROLES DERIVED FROM ACETONYLACETONE.

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Of the methods available for the synthesis of derivatives of pyrrole, one of the oldest and most generally applicable is the Paal-Knorr Synthesis (Knorr, Berichte, 1885, 18, 302; Annalen, 1886, 236, 290; Paal, Berichte, 1885, 18, 367, 2251) in which γ-diketones are condensed with ammonia or primary amines. Much work on this reaction has established that practically any 1:4-diketone capable of forming a di-enol may be used with ammonia; that not all primary amines are suitable; and that acid amines do not react to give N-acyl pyrroles at all. Thus, Paal and Schneider (Berichte, 1886, 19, 3156) examined the behaviour of acetonylacetone and phenacylacetooacetic ester towards certain substances containing the –NH₂ group and showed that they condensed readily with ethylene diamine, trimethylenediamine, m-phenylenediamine, benzidine, glycine, m-aminobenzoic acid, o-aminophenol, and aminoazobenzene, but failed to give pyrroles with urea, oxamide, benzamide, o-nitraniline or sulphanilic acid. They concluded that pyrrole formation would occur only if the amines used were of strong basic character.

That the problem is not so simple as this, however, is shown by later observations of Paal and Braikoff (Berichte, 1889, 22, 3086-95), who found that ethyl phenacetyl benzoylacetate condenses readily with aromatic amines such as aniline, o- and p-toluidines, 4-m-xylidine, α- and β-naphthylamines, o-aminophenol and p-phenylenediamine, but fails to give pyrroles with such relatively strong aliphatic bases.
as ethylamine, allylamine and ethylene diamine. It also fails to give pyrroles with glycine and m-aminobenzoic acid.

These two series of experiments show clearly that the factors governing the formation of pyrroles depend partly on the diketone employed and partly on the amine. That the strength of the amine as a base is not the only factor is also indicated by the work of Borsche and Titsingh (Berichte, 1907, 40, 5011), who studied the condensation of ethyl phenacyl acetoacetate with the isomeric nitroanilines, and found that whereas \( p \) - and \( m \)-nitroanilines could condense to give good yields of the corresponding 1-nitrophenyl pyrroles, \( o \)-nitroaniline condensed only with great difficulty, the yield of pyrrole being very bad even after several day's heating of the components together in glacial acetic acid solution.

It is probable that in the Paal-Knorr reaction the diketone first reacts as a mono-enol with the ammonia or amine present to give an intermediate unsaturated \( \gamma \)-amino ketone. Subsequent enolization of the second ketone group followed by intramolecular linkage of carbon with nitrogen and simultaneous extrusion of a water molecule completes the ring closure.

The intermediate \( \gamma \)-amino ketone may sometimes be isolated by adopting special precautions. Thus, Knorr
and Rabe (*Berichte*, 1900, 33, 3801) isolated 2-amino-Δ²-hexen-5-one-3:4-dicarboxylic diethyl ester by the action of ammonia on diethyl diacetyl succinate in ice-cold ethereal solution. Borsche and Fels (*Berichte*, 1906, 39, 3877), also, have isolated similar intermediates from ethyl phenacyl acetoacetate and from ethyl acetonylbenzoyl acetate.

If the suggested mechanism for the reaction be the true one it might be expected that the early stages of pyrrole formation will be influenced by the degree to which the diketone employed is enolized, and a good deal of attention must be paid to this aspect of the problem in any systematic study of the reaction.

Recent investigation of the by-products obtained in the manufacture of acetic acid from acetylene on the large scale has shown that acetonylacetone is one of the substances produced in the process, and that it accumulates in the high boiling fractions (cf. Benson and Cadenhead, *J. Soc. Chem. Ind.*, 1934, 53, 40-43). In consequence, acetonylacetone has become available in quantity and is now a relatively cheap organic chemical. The arrival of a supply of this simplest γ-diketone has led us to study its condensation with a large number of amines—mainly aromatic—in order to ascertain whether those amines which resist pyrrole formation with it have any significant property in common. In the course of these experiments we have studied the conditions of condensation, and have worked out a useful variation of the method usually utilised by the earlier workers, who heated the components together in glacial acetic acid solution. Following up an observation of Coffey, Thomson, and Wilson (*J.C.S.*, 1936, 856) that acid catalyses the condensation of amines with acetoacetic ester to β-aminocrotonic esters we have found that an equimolecular mixture of acetonylacetone and an aromatic amine such as aniline splits out water very rapidly after addition of a very small amount of 1:1 hydrochloric acid and gentle warming. However, the mineral acid seems to help polymerization, and the products rapidly become red. Boiling glacial acetic acid also causes darkening, when the condensation is carried out in this medium. However, if the components are boiled under reflux in alcoholic solution in presence of a little glacial acetic acid the pyrrole condensation goes quite smoothly, the products are much cleaner, and the yields are good.
Repetition of the experiments of some previous workers has confirmed their observations. Thus, we have confirmed Paal and Schneider’s result (loc. cit.) that urea and o-nitroaniline fail to give any trace of a pyrrole with acetonylacetone, even under widely varied conditions. Tribromoaniline also fails to react and this result may possibly be attributed to steric hindrance, but ortho substituted anilines do not, in general, show any marked reluctance to form pyrroles (cf. Holdsworth and Lions, Journ. Roy. Soc. N.S.W., 1936, 70, 431-6). 2 : 4-Dichloroaniline, also, apparently fails to react.

The most interesting failure we have encountered is that of methyl anthranilate, which gave no pyrrole even under the most widely varied conditions. Anthranilic acid itself reacts very readily with acetonyl acetone to form 1-o-carboxyphenyl-2 : 5-dimethyl pyrrole in good yield. Also, Bock and Adams (J.A.C.S., 1931, 53, 374) heated ethyl acetonyl acetoacetate and anthranilic acid together in alcoholic solution and obtained a 30 per cent. yield of ethyl 1 - o - carboxyphenyl - 2 : 5 - dimethyl pyrrole - 3 - carboxylate within an hour. Anthranilic acid also condenses readily with phenacyl ləuvulinic acid to 1-o-carboxyphenyl-2-phenyl pyrrole 5-β-propionic acid (Holdsworth and Lions, loc. cit.). An attempt to condense o-amino benzamide with acetonyl acetone gave no readily isolable pyrrole, and an attempt to condense an o-aminoacetophenone derivative—6-aminoacetoveratrone—with acetonyl acetone was also a failure. We further attempted the condensation of methyl anthranilate with ethyl phenacyl acetoacetate and with phenacyl ləuvulinic acid without success. The theoretical implications of these failures will be discussed later, when more data has been accumulated. The pyrroles prepared are described below in the experimental section.

Experimental.

Two general methods were employed for the preparation of the derivatives of pyrrole described below.

(A) The amine (approximately 3 grams) was mixed with a slight excess of acetonyl acetone, warming if necessary to obtain a homogeneous solution, and then one small drop of 5N hydrochloric acid was added. When reaction proceeded at room temperature, which was indicated by the almost immediate separation of water globules, the reaction mixture was allowed to stand for about 30 minutes
before being worked up. If there was no rapid separation of water the mixture was heated at 100° for periods varying between one and two hours, according to the rapidity of separation of water globules, and was then cooled. If the product of reaction crystallised it was usually dried on a porous plate and was then recrystallised. Otherwise, it was poured into water, taken up and dried in ether, and, if necessary, distilled under reduced pressure.

(B) Equimolecular quantities of the base (3 grams approximately) and acetonyl acetone were dissolved in a mixture of ethyl alcohol (10 c.c.) and glacial acetic acid (1 c.c.) and the solution then heated under reflux for periods varying between 15 minutes and 4 hours. After cooling, the reaction mixture was poured into water, and the product recovered as in method A.

The yields obtained by both these methods were usually very good. However, the products from method B were usually much cleaner and this method is to be preferred. In method A, after a certain time the product rapidly tends to redden, and it is worthy of note that very few of the pyrroles obtained are particularly stable when exposed to light and air.

1-Phenyl-2 : 5-dimethyl pyrrole.

From aniline and acetonyl acetone. Method A. Recrystallised from methyl alcohol m.p. 51–52°. This substance has been previously prepared by the decarboxylation of 1-phenyl-2 : 5-dimethyl pyrrole-3 : 4-dicarboxylic acid (Knorr, Annalen, 236, 308).

1-o-Toly1-2 : 5-dimethyl pyrrole.

From o-toluidine and acetonyl acetone. Method B. Colourless liquid boiling at 123–125°/22 mm. Found N = 7.8%; calculated for C_{13}H_{15}N, N = 7.6%.

1-m-Tolyl-2 : 5-dimethyl pyrrole.

From m-toluidine and acetonyl acetone. Method B. Recrystallised from methyl alcohol as glistening plates m.p. 55°. This substance has been previously prepared by the decarboxylation of 1-m-tolyl-2 : 5-dimethyl pyrrole-3 : 4-dicarboxylic acid (Bulow, List, Berichte, 1902, 35, 688).

1-p-Tolyl-2 : 5-dimethyl pyrrole.

From p-toluidine and acetonyl acetone. Method A. Recrystallised from methyl alcohol as glistening plates
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m.p. 46°. This substance has been previously prepared by the decarboxylation of 1-p-tolyl-2: 5-dimethyl pyrrole-3 : 4-dicarboxylic acid (Knorr, Berichte, 1885, 18, 309).

1-(2: 4-Dimethyl phenyl)-2 : 5-dimethyl pyrrole.
From 4-m-xylidine and acetonyl acetone. Method B. Colourless fragrant liquid boiling at 136°/10 mm. Found N = 7.1%; calculated for C₁₄H₁₇N, N = 7.0%.

1-(2: 5-Dimethyl phenyl)-2 : 5-dimethyl pyrrole.
From p-xylidine and acetonyl acetone. Method B. Colourless fragrant liquid boiling at 121°/9 mm. Found N = 7.2%; calculated for C₁₄H₁₇N, N = 7.0%.

1-(3'-Acenaphthyl)-2 : 5-dimethyl pyrrole.
From 3-amino acenaphthene and acetonyl acetone. Method B. Recrystallised from ethyl alcohol as faintly brown crystals m.p. 92°. Found N = 5.8%; calculated for C₁₃H₁₅N, N = 5.7%.

1-(3'-Fluorenyl)-2 : 5-dimethyl pyrrole.
From 3-amino-fluorene and acetonyl acetone. Method B. Recrystallised from ethyl alcohol as pink needles m.p. 90–91°. Found N = 5.4%; calculated for C₁₉H₁₇N, N = 5.4%.

1-(α-Naphthyl)-2 : 5-dimethyl pyrrole.
From α-naphthylamine and acetonyl acetone. Method A. Recrystallised from methyl alcohol m.p. 121°. This substance has been previously prepared by the decarboxylation of 1-α-naphthyl-2 : 5-dimethyl pyrrole-3 : 4-dicarboxylic acid (Knorr, Annalen, 236, 308).

1-(β-Naphthyl)-2 : 5-dimethyl pyrrole.
From β-naphthylamine and acetonyl acetone. Method A. Recrystallised from methyl alcohol m.p. 71°. This substance has been previously prepared by the decarboxylation of 1-β-naphthyl-2 : 5-dimethyl pyrrole-3 : 4-dicarboxylic acid (Knorr, Annalen, 236, 306).

1-Ethyl-2 : 5-dimethyl pyrrole.
From ethylamine and acetonyl acetone—reaction proceeded without addition of catalyst. Method A. Colourless liquid boiling at 102°/79 mm. Found N = 11.6%; calculated for C₈H₁₃N, N = 11.4%.

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1-(α-Phenyl ethyl)-2 : 5-dimethyl pyrrole.
From α-phenyl ethylamine and acetonyl acetone. Method B. Distilled at 147–149°/14 mm. and then solidified. Recrystallised from alcohol, colourless prisms m.p. 53°. Found N=7·3%; calculated for C_{14}H_{17}N, N=7·5%.

1-Benzyl-2 : 5-dimethyl pyrrole.
From benzylamine and acetonyl acetone. Method A. Recrystallised from aqueous alcohol as colourless needles m.p. 48°. Found N=7·7%; calculated for C_{18}H_{17}N, N=7·5%.

1-(o-Xenyl)-2 : 5-dimethyl pyrrole.
From α-xenylamine and acetonyl acetone. Method A. Recrystallised from methyl alcohol as colourless plates m.p. 100°. Found N=5·6%; calculated for C_{18}H_{17}Cl, N=5·7%.

1-o-Chlorophenyl-2 : 5-dimethyl pyrrole.
From o-chloroaniline and acetonyl acetone. Method B. Colourless liquid boiling at 135°/15 mm. Found N=6·8%; calculated for C_{12}H_{13}ClN, N=6·8%.

1-m-Chlorophenyl-2 : 5-dimethyl pyrrole.
From m-chloroaniline and acetonyl acetone. Method B. Recrystallised from methyl alcohol as colourless needles m.p. 50°. Found N=7·0%; calculated for C_{12}H_{13}ClN, N=6·8%.

1-m-Bromophenyl-2 : 5-dimethyl pyrrole.
From m-bromaniline and acetonyl acetone. Method A. Recrystallised from methyl alcohol as grey crystals m.p. 74–75°. Found N=5·6%; calculated for C_{12}H_{13}BrN, N=5·6%.

1-p-Bromophenyl-2 : 5-dimethyl pyrrole.
From p-bromaniline and acetonyl acetone. Method A. Recrystallised from aqueous methyl alcohol as grey crystals m.p. 74–75°. Found N=5·6%; calculated for C_{12}H_{13}BrN, N=5·6%.
1-(2:5-Dichlorophenyl)-2:5-dimethyl pyrrole.

From 2:5-dichloraniline and acetonyl acetone. Method B. Pale yellow liquid boiling at 151–153°/16 mm. Found N=5·9%; calculated for C_{12}H_{12}NCl_{2}, N=5·8%.

1-(m-Hydroxyphenyl)-2:5-dimethyl pyrrole.

From m-aminophenol and acetonyl acetone. Method B. Distilled at 178°/10 mm. and solidified on cooling m.p. 58°. Found N=7·6%; calculated for C_{12}H_{13}NO, N=7·5%.

1-(o-Methoxy phenyl)-2:5-dimethyl pyrrole.

From o-anisidine and acetonyl acetone. Method B. Recrystallised from methyl alcohol as white needles m.p. 65°. Found N=7·0%; calculated for C_{13}H_{15}ON, N=7·0%.

1-(p-Methoxy phenyl)-2:5-dimethyl pyrrole.

From p-anisidine and acetonyl acetone. Method A. Recrystallised from methyl alcohol as white needles m.p. 65°. Found N=7·0%; calculated for C_{13}H_{15}ON, N=7·0%.

1-(o-Ethoxy phenyl)-2:5-dimethyl pyrrole.

From o-phenetidine and acetonyl acetone. Method B. Pale yellow liquid boiling at 140°/10 mm. Found N=6·3%; calculated for C_{14}H_{17}NO, N=6·5%.

1-(p-Ethoxy phenyl)-2:5-dimethyl pyrrole.

From p-phenetidine and acetonyl acetone. Method A. Recrystallised from methyl alcohol as colourless plates m.p. 63°. Found N=6·6%; calculated for C_{14}H_{17}NO, N=6·5%.

1-(2:3-Dimethoxy phenyl)-2:5-dimethyl pyrrole.

From 3-amino veratrole and acetonyl acetone. Method B. Recrystallised from aqueous alcohol as white needles m.p. 68°. Found N=5·8%; calculated for C_{14}H_{17}NO_{2}, N=6·1%.

1-(3:4-Dimethoxy phenyl)-2:5-dimethyl pyrrole.

From 4-amino veratrole and acetonyl acetone. Method B. Recrystallised from alcohol as needles m.p. 54–55°. Found N=5·9%; calculated for C_{14}H_{17}NO_{2}, N=6·1%.

1-(3:4-Diethoxy phenyl)-2:5-dimethyl pyrrole.

From 4-amino catechol diethyl ether and acetonyl acetone. Method B. Colourless liquid boiling at
l-l'-m-Phenylene-bis-{2:5-dimethyl pyrrole).
From m-phenylene diamine and acetonyl acetone. Method A. Recrystallised from methyl alcohol as white plates m.p. 106-107°. Found N=10.5% ; calculated for C_{18}H_{28}N_2, N=10.6%.

l-(m-Acetamido phenyl)-2:5-dimethyl pyrrole.
From m-amino acetanilide and acetonyl acetone. Method B. Recrystallised from methyl alcohol as faintly brown plates m.p. 192°. Found N=12.9% ; calculated for C_{14}H_{17}N_2O, N=12.3%.

l-l'-p-Phenylene-bis-(2:5-dimethyl pyrrole).
From p-phenylene diamine and acetonyl acetone. Method A. Recrystallised from benzene as white plates softening at 245°, m.p. 253°. Found P=10.4% ; calculated for C_{18}H_{20}N_2, N=10.6%.

l-(p-Acetamido phenyl)-2:5-dimethyl pyrrole.
From p-amino acetanilide and acetonyl acetone. Method B. Recrystallised from methyl alcohol as faintly pink plates m.p. 207°. Found N=12.6% ; calculated for C_{14}H_{17}N_2O, N=12.3%.

1-1'-(3'3'-dimethyl diphenylene(4:4'))-bis-(2:5-dimethyl pyrrole).
From o-tolidine and acetonyl acetone two molecular parts. Method A. Recrystallised from dioxan m.p. 190°. Found N=7.8% ; calculated for C_{26}H_{28}N_2, N=7.6%.

I-(5'-Quinolinyl)-2:5-dimethyl pyrrole.
From 5-aminoquinoline and acetonyl acetone. Method A. Recrystallised from methyl alcohol m.p. 77°. Found N=12.6% ; calculated for C_{17}H_{14}N_2, N=12.6%.

I-(8'-Quinolinyl)-2:5-dimethyl pyrrole.
From 8-amino quinoline and acetonyl acetone. Method A. Recrystallised from methyl alcohol as pink plates m.p. 143°. Found N=12.8% ; calculated for C_{17}H_{14}N_2.

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1-1'-m-Phenylene-bis-(2 : 5-dimethyl pyrrole).
From m-phenylene diamine and acetonyl acetone two molecular parts. Method A. Recrystallised from alcohol as white plates m.p. 106–107°. Found N = 10·5%; calculated for C_{18}H_{28}N_{2}, N = 10·6%.

1-(m-Acetamido phenyl)-2 : 5-dimethyl pyrrole.
From m-amino acetonilide and acetonyl acetone. Method B. Recrystallised from methyl alcohol as faintly brown plates m.p. 192°. Found N = 12·9%; calculated for C_{14}H_{17}N_{2}O, N = 12·3%.

1-1'-p-Phenylene-bis-(2 : 5-dimethyl pyrrole).
From p-phenylene diamine and acetonyl acetone two molecular parts. Method A. Recrystallised from benzene as white plates softening at 245°, m.p. 253°. Found N = 10·4%; calculated for C_{18}H_{20}N_{2}, N = 10·6%.

1-(p-Acetamido phenyl)-2 : 5-dimethyl pyrrole.
From p-amino acetonilide and acetonyl acetone. Method A. Recrystallised from methyl alcohol as faintly pink plates m.p. 207°. Found N = 12·6%; calculated for C_{14}H_{17}N_{2}O, N = 12·3%.

1-1'-(3-3'-dimethyl diphenylene (4-4'))-bis-(2 : 5-dimethyl pyrrole).
From o-tolidine and acetonyl acetone two molecular parts. Method A. Recrystallised from dioxan m.p. 190°. Found N = 7·8%; calculated for C_{26}H_{28}N_{2}, N = 7·6%.

1-(5'-Quinolinyl)-2 : 5-dimethyl pyrrole.
From 5-aminoquinoline and acetonyl acetone. Method A. Recrystallised from methyl alcohol m.p. 77°. Found N = 12·6%; calculated for C_{17}H_{14}N_{2}, N = 12·6%.

1-(8'-Quinolinyl)-2 : 5-dimethyl pyrrole.
From 8-amino quinoline and acetonyl acetone. Method A. Recrystallised from methyl alcohol as pink plates m.p. 143°. Found N = 12·8%; calculated for C_{17}H_{14}N_{2}, N = 12·6%.

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