BINUCLEAR ISOMERISM OF DIPHENYL TYPE.

PART III.*

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In this paper there are described briefly the results of certain experiments having as their object the preparation of substances which might be expected to occur in enantiomorphous forms, the enantiomorphism being dependent on restriction of rotation of a cyclic nucleus attached to a benzene nucleus or on restriction of rotation of a group of atoms similarly attached. Two of the authors are unable to continue with the work, and it seems desirable at this point to record the results already obtained and to mention briefly the objects of the investigation which will be continued as soon as opportunity affords.

In the first series of experiments it was proposed to prepare and attempt to resolve 1-phenyl-3:5-dimethyl-4-(o-carboxyphenyl) pyrazole (I), which is structurally closely analogous to the 1-(o-carboxyphenyl)-2:5-dimethyl pyrrole-3-carboxylic acid (II) resolved by Bock and Adams (J.A.C.S., 1931, 53, 374).

![Structural formulae](image)

* Part I appeared in This Journal, 1930, 64, 320, Part II in 1933, 67, 178.
Maclean and Adams (J.A.C.S., 1933, 55, 4683) have remarked that "from experience gained in the diphenyl series the methyl grouping may be assumed to be relatively large", and Yuan and Adams (Chem. Rev., 1933, 12, 261) have also made reference to this point. It would thus appear that (I) should exist in enantiomorphous forms. Now Hurtley (J.C.S., 1929, 1870) has shown that sodium o-bromobenzoate can be readily condensed with sodio acetylacetone in alcoholic solution in presence of copper powder to form the sodium salt of 3-(o-carboxyphenyl)-2: 1-pentane dione (III) in good yield. We have found that (III) condenses readily with hydrazines to form pyrazoles. Thus, with hydrazine itself 3: 5-dimethyl-4-(o-carboxyphenyl) pyrazole is rapidly formed. Semi-carbazide reacts with (III) to form 3: 5-dimethyl-4-(o-carboxyphenyl)-pyrazole-1-carboxylic acid amide, a crystalline solid melting at 189°; whilst with phenyl-hydrazine the acid (I), melting at 247°, is rapidly formed. Attempts to resolve this acid proved abortive because of its weakness as an acid and inability to form satisfactory alkaloidal salts (cf. Bock and Adams, J.A.C.S., 1931, 53, 3520).

In consequence, p-carboxyphenylhydrazine was prepared and condensed with (III), so as to obtain 1-(p-carboxyphenyl)-3: 5-dimethyl-4-(o-carboxyphenyl) pyrazole (IV), a dicarboxylic acid melting at 133° which might reasonably be expected to be strong enough to form stable alkaloidal salts. Preliminary experiments have shown that this is so, and a strychnine salt melting at 187° has been isolated in small amount, but so far not further examined. Several other pyrazoles derived from p-carboxyphenylhydrazine and p-carbethoxyphenylhydrazine are also described in the experimental section.

The second part of the work described in this paper consisted of preliminary exploratory experiments with the object of combining some of the ideas of Chang and Adams with those of Mills and his co-workers. Chang and Adams (J.A.C.S., 1934, 56, 2089) prepared several meta and para dipyruryl benzenes and effected the resolution of trans-4: 6-di-(2: 5-dimethyl-3-carboxypyruryl)-1: 3-dimethyl benzene (V).

The enantiomorphism of (V) is dependent on the restriction of rotation of the pyrrole nuclei about the bonds joining them to the benzene ring, caused by the methyl groups attached to the benzene ring. It is worthy of
comment that the stability of the enantiomers is very considerable. Chang and Adams did not discuss the possibility of obtaining ortho dipyrrylbenzenes, although the most interesting feature of the structure of such substances would be that the free rotation of each pyrrole nucleus about the bond joining it to the benzene nucleus would be prevented by the second pyrrole nucleus. Thus, a dipyrryl benzene of the formula (VI) should be obtainable in cis and trans modifications of which the latter should exist in enantiomorphous forms. The possibility of preparation of such substances from o-phenylenediamine has not so far been examined.

Mills and Elliott (J.C.S., 1928, 1291), Mills and Breckenridge (ibid., 1932, 2209), and, more recently, Mills and Kelham (ibid., 1937, 274) have shown that molecular asymmetry due to restriction of rotation about a single bond can be observed among suitably substituted arylamines such as benzene sulphonyl-8-nitro-1-naphthylglycine (VII), 8-benzene sulphonylethylamino-1-ethyl-quinolinium salts (VIII), and N-acetyl-N-methyl-p-toluidine-3-sulphonic acid (IX). The important necessary condition for restriction of rotation of a disubstituted amino group
attached to a benzene nucleus is that the "blocking group" in the ortho position should be sufficiently large. Hence it could hardly be doubted that a trans dipyrrolyl benzene of type (VI) should be resolvable. Further, a disubstituted amino-phenyl pyrrole of type (X) such as a piperidinophenyl pyrrole (XI) or a phthalimidophenyl pyrrole (XII) should exist in enantiomorphous forms, as (XI) and (XII) are types of 2-substituted phenyl pyrroles such as the compound

(II) resolved by Bock and Adams, and the 2-substituent group is relatively large. It is significant that 1-(o-piperidinophenyl)-2:5-dimethyl pyrrole (XI; \( R_3, R_4 = \text{CH}_3 \)), which is described in the experimental portion, cannot be induced to form quaternary ammonium salts although it functions as a base. Conversion of the piperidine nitrogen to the 4-covalent state would demand a tetrahedral disposition of the groups around this nitrogen, and owing to the adjacent pyrrole nucleus this demand cannot be satisfied.

Now in a compound of type (X), whilst free rotation of the pyrrole nucleus will almost certainly be prevented, the possibility that rotation of the disubstituted amino
group about the $>N-$ benzene link will also be restricted, must be considered, and it should be possible to prepare suitable pyrroles of type (X), where the groups $R_3$ and $R_4$ are identical, and the pyrrole nucleus functions simply as a blocking group to prevent the free rotation of the $R_1>N-$ group about the bond joining the nitrogen atom to the benzene nucleus.

It must be remembered that with small groups $R_1$ and $R_2$ (Formula X), although the pyrrole nucleus would be a very effective blocking group, if in the same plane as the benzene ring, its effectiveness would be markedly diminished when the plane of the pyrrole nucleus is at right angles to the plane of the benzene ring, provided that the pyrrole ring is considered a flat ring of ordinary atomic thickness, i.e. without any "bulge". Crystal structure measurements show quite clearly that atoms in different molecules of aromatic substances cannot approach each other nearly as much as atoms bound together in the same molecule, and that to all intents and purposes a benzene ring possesses a "bulge" and cannot be considered as a completely flat hexagon. Hence, analogy suggests that the pyrrole ring also would possess some kind of a "bulge", thus increasing its effectiveness as a blocking group.

It would be important from the point of view of examining the effectiveness of the "bulge" of the benzene ring to prevent free rotation of an ortho nucleus or group to examine some substances of the type (XIII), or even better still to examine certain diphenyl diphenyls of the

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\text{XIII}
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\text{XIV}
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type (XIV), in which space demands should prevent all four benzene rings from being simultaneously coplanar. However, rotation of the rings C and D could allow rings A and B to be simultaneously coplanar (i.e. allow free
rotation about the bond between rings A and B), provided that the "bulge" on each benzene ring C and D was not sufficiently great to interfere with the ortho hydrogen atoms attached to rings A and B.

As further examples of the type of substances examined by Mills and Kelham (loc. cit.) there should be considered substances of the type (XV). We have prepared o-piperidinophenyl phthalimide (XVI), which is of this type except that $R^1$ and $R^2$ are the same (in the phthalimide residue) and also o-piperidinophenyl homophthalimide (XVII). From neither (XVI) nor (XVII) could a quaternary salt be prepared owing to steric hindrance, although both are definite bases. On the other hand 2-acetylaminophenyl piperidine readily forms a methiodide, and it certainly seems probable that (XVII) should be resolvable.

Finally, we report the synthesis of a few new N-phenyl pyrroles, and further failures to obtain pyrroles from o-nitraniline and methyl anthranilate when treated with 1:4-diketones (cf. Hazlewood, Hughes and Lions, J. Proc. Roy. Soc. N.S.W., 1937, 71, 92). There can be little doubt that the latter of these substances particularly is chelated and must almost be regarded as a secondary base, with only one hydrogen atom readily available for substitution. In anthranilic acid, on the other hand, the hydrogen of the carboxyl group is probably concerned in the secondary
valence forces, and the two hydrogens attached to nitrogen are thus available. We also describe the synthesis of 2:5-heptanedione, a simple 1:4-diketone we propose to use in the synthesis of unsymmetrical N-phenyl pyroles.

**Experimental.**

o-Carboxyphenyl acetylacetone (III) was prepared according to the method of Hurtley (J.C.S., 1929, 1870), improvements being effected by using slightly more copper powder, and by removing most of the alcohol from the filtered reaction mixture under reduced pressure before diluting with ice-water and acidifying.

3:5-Dimethyl-4-(o-carboxyphenyl)-pyrazole.

Hydrazine hydrate solution (1 c.c. of 50\%) was added to a solution of (III) (1 g.) in alcohol (10 c.c.) and the solution boiled under reflux for twenty minutes. The solvent was then removed under reduced pressure, the residue dissolved in a little water and 1:1 acetic acid added in very slight excess. The white precipitate formed was collected and recrystallised from dilute alcohol. It came down in colourless prisms melting at 250°.

Found: \( N = 12.9\% \); calculated for \( \text{C}_{12}\text{H}_{12}\text{O}_{2}\text{N}_{2} \), \( N = 12.6\% \). 

1-Phenyl-3:5-dimethyl-4-(o-carboxyphenyl)-pyrazole (I).

Phenylhydrazine (1 g.) was added to a solution of (III) (1 g.) in alcohol (10 c.c.) and the solution boiled under reflux for thirty minutes. Colourless crystals separated on cooling. Recrystallised from alcohol they melted at 247°.

Found: \( N = 9.8\% \); calculated for \( \text{C}_{18}\text{H}_{16}\text{O}_{2}\text{N}_{2} \), \( N = 9.6\% \). 

4-Carboxyphenylhydrazine.

The method of Fisher (Annalen, 1882, 212, 337) was modified in that, after reduction of p-carboxyphenyl-diazonium chloride with sulphurous acid and zinc dust and filtration, an equal volume of concentrated hydrochloric acid was added to the filtrate instead of saturating with dry hydrogen chloride. The free hydrazine, also, was recovered from its hydrochloride by addition of sodium acetate solution to its boiling aqueous solution, followed by
was collected and recrystallised from aqueous alcohol and thus obtained as colourless prisms melting at 133°. Found: C=67-7, H=4-9, N=8-5%; calculated for $\text{C}_{19}\text{H}_{16}\text{O}_{4}\text{N}_{2}$, C=67-8, H=4-8, N=8-3%.

3: o-Dimethyl-1-(p-carbethoxyphenyl)-pyrazole.

A solution containing p-carbethoxyphenylhydrazine (1-8 g.) and acetylacetone (1 g.) in alcohol (15 c.c.) was refluxed for thirty minutes, freed of solvent, and the residue treated with water and a little dilute acetic acid. A yellow oil was precipitated but this soon solidified. Recrystallised from aqueous alcohol it was obtained in pale yellow prisms melting at 65°. Found: N=11.7%; calculated for $\text{C}_{14}\text{H}_{16}\text{O}_{2}\text{N}_{2}$, N=11.5%.

1- (p-Carbethoxyphenyl)-3:5-dimethyl-4-(o-carboxyphenyl)-pyrazole.

A solution of (III) (1-1 g.) and p-carbethoxyphenylhydrazine (0-9 g.) in alcohol (20 c.c.) was boiled for thirty minutes, then freed from solvent and ice-water added to the residual oil, which then soon solidified. It was recrystallised from aqueous alcohol and obtained in faintly yellow minute prisms melting at 139°. Found: N=7.8%; calculated for $\text{C}_{21}\text{H}_{20}\text{O}_{4}\text{N}_{2}$, N=7.7%.

3: 5-Dimethyl-4-(o-carboxyphenyl)-pyrazole-1-carboxylic Acid Amide.

To a solution of (III) (1-1 g.) in alcohol (10 c.c.) was added a solution of semicarbazide hydrochloride (0-6 g.) and sodium acetate (0-7 g.) in a little water, and after thorough mixing the mixture was allowed to stand. A precipitate commenced to form after a few hours, and it was collected after 24 hours' standing and recrystallised from boiling water. Minute colourless prisms melting at 189° were obtained. Found: N=16.4%; calculated for $\text{C}_{13}\text{H}_{13}\text{O}_{3}\text{N}_{3}$, N=16.2%.

1-3-Diketo-2-(o-piperidinophenyl)-1:2:3:4-tetrahydro isoquinoline (XVII).

Homophthalic acid (18 g.) and 2-aminophenyl piperidine (17.6 g.) were carefully mixed and heated to 180° for fifteen minutes. The solvent was then removed under reduced pressure, and the residue treated with water and a slight excess of 1:1 acetic acid. The white solid which separated was collected and recrystallised from aqueous alcohol, being obtained in colourless needles, m.p. 158°.

Found: N=13.3%; calculated for $\text{C}_{12}\text{H}_{12}\text{O}_{2}\text{N}_{2}$, N=13.0%.

3: 5-Dimethyl-1-(p-carboxyphenyl)-pyrazole.

Acetylacetonc (0.6 g.) and p-carboxyphenylhydrazine (1 g.) were warmed together in alcohol solution (10 c.c.) for thirty minutes. The solvent was then removed under reduced pressure, and the residue treated with water and a slight excess of 1:1 acetic acid. The white solid which separated was collected and recrystallised from aqueous alcohol, being obtained in colourless needles, m.p. 158°.

Found: N=13.3%; calculated for $\text{C}_{12}\text{H}_{12}\text{O}_{2}\text{N}_{2}$, N=13.0%.

1- (p-Carboxyphenyl) - 3: 5 - dimethyl - 4 - (o-carboxyphenyl)-pyrazole (IV).

p-Carboxyphenylhydrazine (3.2 g.) and (III) (4.5 g.) were dissolved in absolute alcohol (50 c.c.) and heated under reflux for three hours. The alcohol was then removed under reduced pressure, water and a slight excess of dilute acetic acid added, and the mixture cooled in ice. A white crystalline precipitate (6 g.; 90% of theory) separated,
was collected and recrystallised from aqueous alcohol and thus obtained as colourless prisms melting at 133°.

Found: C=67.7, H=4.9, N=8.5%; calculated for C₁₉H₁₆O₄N₂, C=67.8, H=4.8, N=8.3%.

3: 5-Dimethyl-1-(p-carbethoxyphenyl)-pyrazole.

A solution containing p-carbethoxyphenylhydrazine (1.8 g.) and acetylacetone (1 g.) in alcohol (15 c.c.) was refluxed for thirty minutes, freed of solvent, and the residue treated with water and a little dilute acetic acid. A yellow oil was precipitated but this soon solidified. Recrystallised from aqueous alcohol it was obtained in pale yellow prisms melting at 65°.

Found: N=11.7%; calculated for C₁₄H₁₅O₂N₂, N=11.5%.

1-(p-Carbethoxyphenyl) 3: 5-dimethyl-4-(o-carboxyphenyl)-pyrazole.

A solution of (III) (1.1 g.) and p-carbethoxyphenylhydrazine (0.9 g.) in alcohol (20 c.c.) was boiled for thirty minutes, then freed from solvent and ice-water added to the residual oil, which then soon solidified. It was recrystallised from aqueous alcohol and obtained in faintly yellow minute prisms melting at 139°.

Found: N=7.8%; calculated for C₂₁H₂₀O₄N₂, N=7.7%.

3: 5-Dimethyl-4-(o-carboxyphenyl)-pyrazole-1-carboxylic Acid Amide.

To a solution of (III) (1.1 g.) in alcohol (10 c.c.) was added a solution of semicarbazide hydrochloride (0.6 g.) and sodium acetate (0.7 g.) in a little water, and after thorough mixing the mixture was allowed to stand. A precipitate commenced to form after a few hours, and it was collected after 24 hours' standing and recrystallised from boiling water. Minute colourless prisms melting at 189° were obtained.

Found: N=16.4%; calculated for C₁₃H₁₃O₃N₃, N=16.2%.

1: 3-Diketo 2-(o-piperidinophenyl) 1: 2: 3: 4-tetrahydro isoquinoline (XVII).

Homophthalic acid (18 g.) and 2-aminophenyl piperidine (17.6 g.) were carefully mixed and heated to 180° for fifteen
minutes. The mass frothed up and then became a quiescent orange liquid, whilst water was evolved. On cooling, an orange coloured very viscous gum remained which rapidly crystallised on rubbing with cold alcohol. It was recrystallised from boiling alcohol and thus obtained in beautiful colourless prisms which melted at 143°.

Found: C = 74.7, H = 6.1, N = 9.0%; calculated for C_{20}H_{20}O_{2}N_{2}, C = 75.0, H = 6.3, N = 8.8%.

Attempts to prepare quaternary ammonium derivatives of this substance all proved abortive. Addition of one drop of piperidine to a solution of this base (1.5 g.) and benzaldehyde (0.7 g.) in alcohol (20 c.c.) led to darkening in colour and evolution of heat. After standing for two days golden yellow prisms of the benzylidene derivative had separated. They were collected and recrystallised from alcohol when they melted at 160-161°.

Found: C = 79.2, H = 5.8%; calculated for C_{22}H_{22}O_{4}N, C = 79.4, H = 5.9%.

2 : 4-Dinitro-2'-piperidinodiphenylamine.

2 : 4-Dinitrochlorobenzene (10.2 g.) and 2-aminophenylpiperidine (8.8 g.) were mixed and heated together on the water-bath for three hours. The fused mixture rapidly became red in colour. After cooling, the viscous melt was rubbed with alcohol, when it rapidly crystallised in orange crystals. These were treated with ammonia and soon became bright scarlet in colour, owing to formation of the free base, which was collected and recrystallised from alcohol. The base came out in magnificent, gleaming, scarlet needles about one centimetre in length, and is the most beautiful crystalline substance the authors have encountered. It melted at 174°.

Found: C = 59.3, H = 5.1, N = 16.6%; calculated for C_{17}H_{18}O_{4}N_{4}, C = 59.6, H = 5.3, N = 16.4%.

2 : 4-Diamino-2'-piperidinodiphenylamine.

Stannous chloride, hydrochloric acid, and metallic tin in slight excess were added to a solution of the nitro compound in boiling alcohol. After some time the alcohol was boiled off, water added, and the solution treated with decolourising charcoal and filtered. Sodium hydroxide solution in excess was added to the cooled filtrate. The undissolved solid was collected and extracted several times with ether.
The combined ethereal extracts were dried and the ether removed. The residual brownish solid was then crystallised from ethylacetate and obtained in very pale brown prisms melting at 157°.

Found: \( N = 20 \cdot 3\% \); calculated for \( \text{C}_{17}\text{H}_{22}\text{N}_{4} \), \( N = 20 \cdot 0\% \).

**Ethyl-1-\( \alpha \)-veratryl-2-methyl-5-phenyl pyrrole-3-carboxylate.**

A solution of ethyl phenacylacetoacetate (2.5 g.) and 4-amino-veratrole (1.55 g.) in alcohol (10 c.c.) and glacial acetic acid (1 c.c.) was refluxed for 90 minutes then poured into water. The brown solid which separated was recrystallised from alcohol with the help of decolourising charcoal and obtained in white glistening plates melting at 115°.

Found: \( N = 3 \cdot 8\% \); calculated for \( \text{C}_{22}\text{H}_{23}\text{O}_{4}\text{N} \), \( N = 3 \cdot 8\% \).

**Ethyl-1-(\( \alpha \)-carboxyphenyl)-2-methyl-5-phenyl pyrrole-3-carboxylate.**

A solution of anthranilic acid (2.75 g.) and ethyl phenacylacetoacetate (5 g.) in alcohol (20 c.c.) and glacial acetic acid (2 c.c.) was heated gently under reflux for nine hours. It was then poured into water and extracted with ether. The solvent was removed from the washed and dried ethereal extract, and the dark brown oily residue which crystallised on standing was recrystallised from acetic acid. It was thus obtained in fine white needles melting at 110°.

Found: \( N = 4 \cdot 2\% \); calculated for \( \text{C}_{21}\text{H}_{19}\text{O}_{4}\text{N} \), \( N = 4 \cdot 1\% \).

**Ethyl-1-(\( \alpha \)-xenyl)-2-methyl-5-phenyl pyrrole-3-carboxylate.**

A solution of 2-aminodiphenyl (1.7 g.), ethyl phenacylacetocacetate (2.5 g.) and glacial acetic acid (1 c.c.) in alcohol (30 c.c.) was refluxed for two hours, then poured into water. A purple oil separated, and was taken up, washed and dried in ether. After removal of the solvent and allowing to stand the residue crystallised and was obtained pure by recrystallisation from boiling alcohol in small colourless prisms melting at 150–151°.

Found: \( N = 3 \cdot 7\% \); calculated for \( \text{C}_{26}\text{H}_{23}\text{O}_{2}\text{N} \), \( N = 3 \cdot 6\% \).
1-(o-Piperidinophenyl)-2 : 5-dimethylpyrrole (XI ; \( R_3, R_4 = CH_3 \)).

An alcoholic solution of equimolecular quantities of acetonylacetone and 2-aminophenylpiperidine containing a little glacial acetic acid was refluxed for two hours, then poured into water. The solid which separated was collected and recrystallised from alcohol and was thus obtained in good yield in small colourless prisms melting at 72°C.

Found: N = 11·2%; calculated for \( C_{17}H_{22}N_2 \), N = 11·0%.

This substance fails to give a methiodide with excess methyl iodide in a sealed tube at 100°C, and apparently, also, does not form a methosulphate.

1-(o-Piperidinophenyl)-2-phenylpyrrole-5-β-propionic Acid.

A solution of phenacyllävulinc acid (3·5 g.) and 2-aminophenylpiperidine (4·7 g.) in alcohol (25 c.c.) containing glacial acetic acid (2 c.c.) was refluxed for 14 hours, then poured into ice-water. A yellowish brown oil was precipitated, and gradually solidified. It was very soluble in alcohol, acetic acid, acetone, and methyl ethyl ketone but insoluble in water. Eventually it was satisfactorily recrystallised from benzene, m.p. 151°C.

Found: N = 7·5%; calculated for \( C_{24}H_{28}O_2N_2 \), N = 7·5%.

The acidic properties of this substance were not very marked. It was not possible to form alkaloidal salts with it.

Ethyl 1-(o-piperidinophenyl)-2-methyl-5-phenylpyrrole-3-carboxylate.

A solution of 2-aminophenylpiperidine (3·5 g.) and ethyl phenacylacetate (5 g.) in alcohol (40 c.c.) containing glacial acetic acid (2 c.c.) was refluxed for three hours, then poured into water. An oily solid separated, and was taken up, washed and dried in ether. After removal of the solvent a very dark oil remained, but this solidified on triturating with alcohol. It was recrystallised from alcohol with the aid of decolourising charcoal and obtained in small white granules melting at 102–103°C.

Found: N = 7·2%; calculated for \( C_{25}H_{28}O_2N_2 \), N = 7·2%.
separated, washed and dried and the solvent removed. The residual oil was then fractionated in vacuo. Most of the excess ethyl acetoacetate was recovered and two fractions boiling at 110-138°/26 mm. (39 g.) and 138-145°/26 mm. (264 g.) were collected. Redistillation of the first fraction afforded a further 20 grams of the second fraction making the total yield approximately 67% of theory. When redistilled ethyl α-acetyl-β-propionyl propionate boils at 140°/26 mm. Its boiling point at 760 mm. is 251°.

Found: 0=60-1, H=7-8%; calculated for C_{19}H_{18}O_{2}N_{2}, 0=60-0, H=8-0%.

2: 5-Heptanone.

Ethyl α-acetyl-β-propionyl propionate.

The method employed was an adaptation of Youitz and Perkins's (J.A.C.S., 1929, 51, 3511-6) modification of the original method of Willstätter and Clark (Berichte, 1914, 47, 291-310) for the preparation of αβ-diacetyl butyric ester. Sodium (48 g.) was finely granulated and stirred with dry ether (200 c.c.). Ethyl acetooacetate (470 g.; 80% excess) together with dry ether (300 c.c.) was then gradually added (one hour). Stirring was continued until the sodium had dissolved completely (14 hours) more ether (500 c.c.) being added from time to time. 1-Chloro-butane-2-one (237 g.) was then slowly added. The sodium salt appeared to dissolve and after a short time heat was evolved and sodium chloride commenced to precipitate. The stirring of the mixture was continued for a further ten hours. Water was then added, the ether layer
separated, washed and dried and the solvent removed. The residual oil was then fractionated in vacuo. Most of the excess ethyl acetoacetate was recovered and two fractions boiling at 110–138°/26 mm. (39 g.) and 138–145°/26 mm. (264 g.) were collected. Redistillation of the first fraction afforded a further 20 grams of the second fraction making the total yield approximately 67% of theory. When redistilled ethyl \(x\)-acetyl-\(\beta\)-propionyl propionate boils at 140°/26 mm. Its boiling point at 760 mm. is 251°.

Found: C = 60.1, H = 7.8%; calculated for \(C_{16}H_{16}O_4\), C = 60.0, H = 8.0%.

2:5-Heptanedione.

Ethyl \(x\)-acetyl-\(\beta\)-propionyl propionate (250 g.) was refluxed for several hours with a solution of potassium carbonate (200 g.) in water (800 c.c.). After cooling, ether was added and the upper layer separated. The aqueous layer was again extracted several times with ether and the combined ethereal extracts were dried and the solvent removed. The residual diketone was then fractionated in vacuo. A colourless oil (100 g.; 63% of theory) boiling at 89–92°/21 mm. was collected. On redistillation it boiled constantly at 90°/21 mm. Its boiling point at 760 mm. is approximately 194°.

Found: C = 65.3, H = 9.2%; calculated for \(C_7H_{12}O_2\), C = 65.6, H = 9.4%.

When treated with semicarbazide this diketone forms a very insoluble semicarbazone melting at 231°.

1-(\(\beta\)-Naphthyl)-2-methyl-5-ethyl pyrrole.

2:5-Heptanedione (2 g.) and \(\beta\)-naphthylamine (2.1 g.) were heated for one hour in solution in alcohol (15 c.c.) containing glacial acetic acid (1 c.c.). The solution was then poured into water and the separated solid collected and recrystallised from aqueous alcohol with the help of decolourising charcoal. It formed lustrous colourless plates melting at 102°.

Found: N = 6.1%; calculated for \(C_{17}H_{17}N\), N = 6.0%.

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Among the methods available for the preparation of acridines is the important synthesis of benzacridines from (3-naphthol, an aromatic amine and an aldehyde, developed by Ullmann and his co-workers (cf. e.g. Ullmann and Naef, Berichte, 1900, 33, 905-919; Ullmann, Racovitza and Rozenband, ibid., 1902, 35, 316; D. R. PP. 117472, 119573, 123260). Ullmann, Rozenband, Muhlhauser and Grether (Berichte, 1902, 35, 326) observed that benzaldehyde, (3-naphthol, and m-phenylene diamines gave very good yields of benzacridines; and, later, Ullmann and Fitzenkam (Berichte, 1905, 38, 3787) extended the reaction to m-aminophenols and m-aminophenol ethers with almost equal success.

It appeared, therefore, that it should be readily possible to condense 4-aminoveratrole with p-naphthol and various aromatic aldehydes, and so to obtain derivatives of 9:10-dimethoxy-1:2-benzacridine. (The American Chemical Society's system of numbering has been adopted for the compounds described in this paper.)

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