1323. *Studies in the Indole Series. Part III.*[1] *The Japp–Klingemann Reaction*

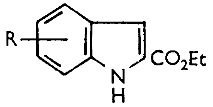
By B. Heath-Brown and P. G. Philpott

A number of indoles have been prepared by the Fischer cyclisation method. The intermediate hydrazones were made by the Japp–Klingemann reaction, in the course of which several new azo-esters were obtained. These little-known compounds are characterised by analysis and by infrared and ultraviolet spectra.

In the course of our work on tryptamines and indolylalkylamines it was necessary to prepare various substituted indoles, some of them in fairly large quantities. While preparations of some of the compounds described below have already appeared in the literature, we have been able to improve them and at the same time take the opportunity to examine some of the intermediate compounds more closely. 5-Benzyloxy-7-methylindole has been prepared for the first time.

The indoles were prepared by Fischer cyclisation of the arylhydrazones (I), to yield the esters (II), which were hydrolysed and the resulting acids decarboxylated by heating in quinoline in the presence of copper chromite.

$Ar.NH{\cdot}N{:}CMe{\cdot}CO_2Et$
(I)



(II) R = alkyl, halogen, MeO, etc.

The hydrazones (I) may be prepared directly from ethyl pyruvate and hydrazines but are more generally available by the Japp–Klingemann reaction, in which the appropriate diazonium salt is coupled with ethyl α-methylacetoacetate under neutral or slightly acid conditions, with loss of the acetyl group. This reaction has been reviewed,[2] and other workers [3-5] have examined it in recent years.

Although it is well known that the azo-esters (III) are formed as intermediates in these reactions, few of them have actually been isolated because they are so readily converted into hydrazones, or their transformation products, which have usually been required instead. For this reason the crude products of certain Japp–Klingemann reactions have been regarded as hydrazones, not always with justification. Thus, in the preparation of 5-benzyloxyindole from *p*-benzyloxybenzenediazonium chloride and ethyl α-methylacetoacetate, Boehme [6] refers to " the crude red liquid phenylhydrazone " and Ash and Wragg [7] describe the product as being " ethyl pyruvate *p*-benzyloxyphenylhydrazone; a red oil." The pure crystalline *p*-benzyloxyphenylhydrazone of ethyl pyruvate (IV) has, in fact, been obtained,[8] in a Japp–Klingemann reaction using diethyl methyloxaloacetate (diethyl oxalopropionate). Although it was apparently found that only the oxalo-ester gave the solid hydrazone, they evidently considered the possibility that the red oils of Boehme, and of Ash and Wragg might contain azo-esters, but they did not obtain these compounds.

In contrast to this, we have shown that in the Boehme–Ash–Wragg synthesis the product consists exclusively of the azo-ester (III). This was readily proved by examining the infrared spectrum of the crude product, which showed two strong carbonyl peaks and

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[1] Part II, A. Cohen and B. Heath-Brown, preceding Paper.
[2] R. R. Phillips, *Org. Reactions*, 1959, **10**, 143.
[3] H. Henecka, H. Timmler, R. Lorenz, and W. Geiger, *Chem. Ber.*, 1957, **90**, 1060.
[4] H. C. Yao and P. Resnick, *J. Amer. Chem. Soc.*, 1962, **84**, 3514.
[5] B. Eistert and M. Regitz, *Annalen*, 1963, **666**, 97; *Chem. Ber.*, 1963, **96**, 2290, 2304, 3120.
[6] W. R. Boehme, *J. Amer. Chem. Soc.*, 1953, **75**, 2502.
[7] A. S. F. Ash and W. R. Wragg, *J.*, 1958, 3889.
[8] B. Marchand, C. Streffer, and H. Jauer, *J. prakt. Chem.*, 1961, **13**, 54.

no NH bands. The ultraviolet spectrum showed a single maximum at 314—315 mμ with a minimum at 255 mμ, being entirely different from that of the hydrazone (see below).

The azo-ester (III) was surprisingly stable and could be distilled *in vacuo* in small quantities without appreciable change. Under mild treatment with 10% ethanolic phosphoric acid the acetyl group was lost and the hydrazone (IV) was obtained, identical with that of Marchand *et al.*[8] Its ultraviolet spectrum had maxima at 308 and 339 mμ, with minima at 265 and 317 mμ. Under vigorous acidic conditions (hot ethanolic hydrogen chloride) both the azo-ester and the hydrazone yielded ethyl 5-benzyloxyindole-2-carboxylate (VII). In the case of the azo-ester, ethyl acetate was formed in addition to the ammonium chloride produced by Fischer cyclisation.

All these reactions were duplicated when starting with 4-benzyloxy-2-methylbenzenediazonium chloride, this leading to the ester (VIII) and eventually to 5-benzyloxy-7-methylindole (IX).

$R\cdot C_6H_4\cdot N{:}N\cdot CMe(COMe)\cdot CO_2Et$

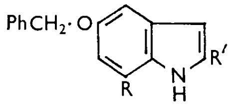
(III: $R = p\text{-}PhCH_2\cdot O$)

(V: $R = p\text{-}MeO$)

$R\cdot C_6H_4\cdot NH\cdot N{:}CMe\cdot CO_2Et$

(IV: $R = p\text{-}PhCH_2\cdot O$)

(VI: $R = p\text{-}MeO$)



(VII: $R = H, R' = CO_2Et$)

(VIII: $R = Me, R' = CO_2Et$)

(IX: $R = Me, R' = H$)

5-Methoxyindole was prepared recently [9] on a 1 mole scale; considerable detail was given for the Japp–Klingemann stage but the resulting intermediate was cyclised without being identified.

We found that the crude product of this reaction consists entirely of the azo-ester (V). It had similar spectral characteristics to the benzyloxy-compound, could be distilled unchanged, and could be converted into the hydrazone (VI) by mild acid treatment. This hydrazone had previously been made by the Japp–Klingemann method, but no details were given of the preparation.[10]

Treatment of the azo-ester with ethanolic hydrogen chloride yielded ethyl 5-methoxyindole-2-carboxylate with liberation of ethyl acetate.

Unlike the above reactions, the Japp–Klingemann reaction with *p*-chlorobenzenediazonium chloride yielded a mixed product which contained the hydrazone (X) as well as the azo-ester (XI). This hydrazone has already been obtained in a Japp–Klingemann reaction with a reported yield of 65%.[11] In our case the yield was only 13% but the combined total of hydrazone and azo-ester was 95%. The two compounds were readily separated by making use of the solubility of the azo-ester in light petroleum in which the hydrazones were insoluble. This appears to be a generally useful difference, even the azo-ester (III) and the related compound from 4-benzyloxy-2-methylaniline being soluble in petroleum on slight warming.

The azo-ester (XI) distilled readily, and its infrared spectrum again showed the two carbonyl bands and no NH group. It was converted into the hydrazone to some extent by standing in ethanol solution, and this change was accelerated in the presence of hydrogen chloride. It is interesting to note that the resulting hydrazone (X) could not be cyclised with ethanolic hydrogen chloride, in contrast to the *p*-benzyloxy- and *p*-methoxy-substituted hydrazones (IV) and (VI), but was cyclised readily by polyphosphoric acid. (Cf. ref. 12.)

The Japp–Klingemann reaction with 2,4-dichlorobenzenediazonium chloride also yielded two products. Although the hydrazone (XII) had been obtained [13] from the

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[9] T. Kralt, W. J. Asma, H. H. Haeck, and H. Moed, *Rec. Trav. chim.*, 1961, **80**, 313; and cf. H. W. Murphy, *J. Pharm. Sci.*, 1964, **53**, 272.

[10] H. N. Rydon and S. Siddapa, *J.*, 1951, 2467.

[11] H. N. Rydon and J. C. Tweddle, *J.*, 1955, 3501.

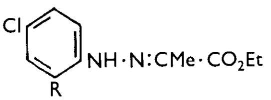
[12] E. H. P. Young, *J.*, 1958, 3495.

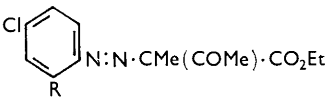
[13] G. Pappalardo and T. Vitali, *Gazzetta*, 1958, **88**, 1147.

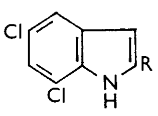
hydrazine and ethyl pyruvate, the azo-ester (XIII) has not been described before; its properties correspond to those of the monochloro-derivative. These dichloro-derivatives were cyclised with polyphosphoric acid, and the resulting ester (XIV) was converted into 5,7-dichloroindole (XV) by hydrolysis and decarboxylation. The properties of our indole and of the intermediates agree with those of the previous workers,[13] who, however, gave few details of their preparation.

The Japp–Klingemann reaction with 2-methylbenzenediazonium chloride gave almost entirely the azo-ester which could be distilled, but the distillation residue yielded a small quantity of an *o*-tolylhydrazone, m. p. 74—76°, which differed from the hydrazone, m. p. 58—60°, made by acid treatment of the azo-ester.

The structures of these compounds are discussed below. Since the azo-esters had been obtained with several substituted diazonium salts it was of interest to examine the unsubstituted compound (XVI). Although this was the intermediate ester in the original work of Japp and Klingemann [14] it had never previously been isolated. We obtained it in 82·5% yield, under conditions given in detail in the Experimental section, as a yellow distillable oil, soluble in petroleum and having the expected infrared characteristics. After our work was completed, a Paper appeared in which this azo-ester was obtained as the result of a Japp–Klingemann reaction using pyridine as solvent.[4] Although differing slightly in the position of the ultraviolet maximum, our product was clearly the same. Treatment with ethanolic hydrogen chloride caused conversion into the corresponding hydrazone, no Fischer cyclisation occurring with this reagent (cf. ref. 15).

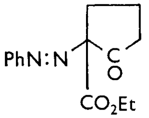

(X : R = H)
(XII: R = Cl)

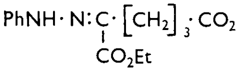

(XI : R = H)
(XIII : R = Cl)

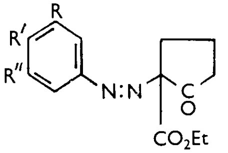

(XIV : R = CO$_2$Et)
(XV : R = H)

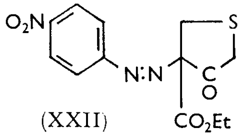
When 2-ethoxycarbonylcyclopentanone was substituted for ethyl α-methylacetoacetate in the above Japp–Klingemann reaction the product (XVII) was obtained. This also has been reported recently.[4] Under conditions different from ours this Japp–Klingemann reaction [16] yielded a product, after acid treatment, which was thought to be the hydrazone (XVIII), but it was cyclised without further examination. It had also been observed [17] that an intermediate azo-ester was produced in this reaction, but again this was not purified. However, in a later Paper,[18] the isolation and purification of the three substituted azo-esters (XIX)—(XXI) all of which were crystalline solids, was described. Very recently [5] the crystalline azo-ester (XXII) and others with similar constitutions were obtained.

PhN:N·CMe(COMe)·CO$_2$Et
(XVI)


(XVII)


$\mathrm{PhNH{\cdot}N{:}\underset{CO_2Et}{C}{\cdot}[CH_2]_3{\cdot}CO_2H}$
(XVIII)


(XIX : R = R″= H, R′= NO$_2$)
(XX : R = R′= R″ = I)
(XXI : R = R″= I, R′= MeO)


(XXII)

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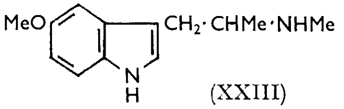
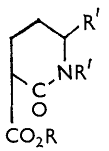
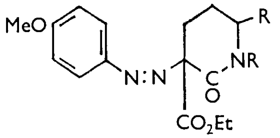
[14] F. R. Japp and F. Klingemann, *Ber.*, 1887, **20**, 2942.
[15] J. Elks, D. F. Elliott, and B. A. Hems, *J.*, 1944, 630.
[16] R. H. F. Manske and R. Robinson, *J.*, 1927, 240.
[17] L. Kalb, F. Schweizer, and G. Schimpf, *Ber.*, 1926, **59**, 1858.
[18] L. Kalb, F. Schweizer, H. Zellner, and E. Berthold, *Ber.*, 1926, **59**, 1860.

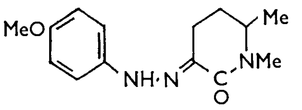
The synthesis of 5-methoxy-3-2′-methylaminopropylindole (XXIII) by the Abramovitch route was described in Part I.[19] One stage of this involved the coupling of *p*-methoxybenzenediazonium chloride with the acid (XXIV), yielding two isomeric hydrazones (XXV). We also tried to couple the diazonium salt with the ethyl ester (XXVI) but under our general conditions no reaction occurred; there was also no coupling reaction with benzenediazonium chloride.

p-Methoxybenzenediazonium chloride had been coupled[3] with the ester (XXVII) under weakly alkaline conditions, yielding the azo-ester (XXVIII), but we were unable to repeat this result when using the homologous ester (XXVI); the addition of N-sodium hydroxide as described[3] caused complete hydrolysis of the ethyl ester as shown by the drop in pH soon after each addition had been made. Only tarry products were isolated. This difficulty was overcome by using potassium carbonate solution instead of sodium hydroxide, as under these conditions slow coupling did take place and we were able to isolate some of the azo-ester (XXIX) as a gum, which could be distilled with slight decomposition. Its constitution was shown by the infrared spectrum, showing both lactam and ester bands and lacking NH bands. Both the isomeric hydrazones (XXV) were isolated as well.


(XXIII)

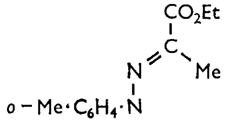

(XXIV: R = H, R′ = Me)
(XXVI: R = Et, R′ = Me)
(XXVII: R = Et, R′ = H)

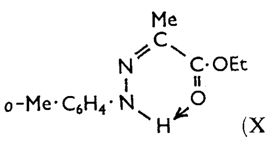

(XXVIII: R = H)
(XXIX: R = Me)


(XXV)

The infrared characteristics of the azo-esters have been referred to above. Details of ultraviolet spectra are given in the Experimental section. Compounds (XIII), (XVI), (XVII), and (XXIX) were examined between 400 and 750 mμ; compound (XVII) showed a small maximum at 400 mμ (log ε 2·30) but otherwise there was insignificant absorption in this region. Low maxima at 400 mμ had been reported and attributed to the azo-chromophore.[3]

The hydrazones obtained from the azo-esters by acid treatment were isolated as single substances except in the case of the *o*-tolylhydrazone mentioned earlier. In this case the hydrazone, m. p. 74—76°, with ultraviolet maximum at 318 mμ is considered to have the structure (XXX), whereas the isomer, m. p. 58—60°, with ultraviolet maximum at 350—351 mμ must be (XXXI) (cf. ref. 3).


(XXX) α-form


(XXXI) β-form

The remaining hydrazones, with one exception, probably have the α-form since their principal maxima lie between 323 and 339 mμ. The exception is the hydrazone made from 4-benzyloxy-2-methylbenzenediazonium chloride [cf. (IV) with Me group *ortho* to NH·N] which could have the β-form since its principal maximum is as high as 368 mμ.

Whilst Fischer cyclisation of the azo-esters and hydrazones has not been discussed in

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[19] Part I. B. Heath-Brown and P. G. Philpott, *J.*, 1965, 7165.

detail, the particular case of the β-*o*-tolylhydrazone is of interest. Cyclisation with polyphosphoric acid followed by hydrolysis and decarboxylation of the derived indole-2-carboxylic ester gave, in addition to the crystalline 7-methylindole (cf. ref. 20) a non-crystalline residue, the analysis and infrared spectrum of which corresponded to a *C*-methylindole. Gas chromatography showed it to be a mixture of 7-methylindole with either 4- or 5-methylindole (by comparison with the gas chromatogram of authentic samples). The melting points of the picrates exclude the latter possibility. The formation of 4-methylindole implies an *ortho*-migration of the methyl group if the cyclisation occurred on to the carbon atom previously occupied by the methyl group or a *para*-migration if the cyclisation occurred on to the vacant *ortho*-position (cf. ref. 21).

EXPERIMENTAL

Solvents and reagents were as described in Part I.[19] Spectra were determined with the same instruments as in Part I; ultraviolet spectra are for ethanol solutions and infrared spectra for solutions in carbon tetrachloride.

Ethyl α-Methyl-α-(phenylazo)acetoacetate. General conditions.—A benzenediazonium chloride solution was made from aniline (9·3 g., 0·1 mole), concentrated hydrochloric acid (25·5 ml., 0·3 mole), water (40—45 ml.), and sodium nitrite (7·6 g., 0·11 mole), and the solution was partially neutralised with crystalline sodium acetate (10·9 g., 0·08 mole). This solution was kept at 0° while ethyl α-methylacetoacetate (15·8 g., 0·11 mole) in ethanol (100 ml.) was treated at 0° with a solution of potassium hydroxide (7·2 g., 0·11 mole; 85—88% KOH) in water (10 ml.) followed at once by ice (100—200 g.). The diazo-solution was then added immediately, with stirring, and the pH was adjusted to 5. A yellow oil formed. After stirring for 2 hr. at 0° the product was extracted with light petroleum (b. p. 40—60°). The extract yielded the crude ester (23·8 g.) which distilled as a yellow liquid, b. p. 104°/0·02 mm., n_D^{20} 1·5230 (20·5 g., 82·5%) (Found: C, 63·1; H, 6·7; N, 11·4. Calc. for $C_{13}H_{16}N_2O_3$: C, 62·9; H, 6·5; N, 11·3%), $\nu_{max.}$ 1750, 1725 cm.$^{-1}$ (CO), no NH bands, $\lambda_{max.}$ 217, 275, $\lambda_{min.}$ 239 mμ (log ε 4·03, 4·00, and 3·64 [lit.,[4] b. p. 138—140°/4 mm., n_D^{22} 1·5158, $\lambda_{max.}$ 272 (log ε 3·85)].

On boiling with 3N-ethanolic hydrogen chloride for 2 hr. ethyl pyruvate phenylhydrazone, m. p. 118—119° (64%) was obtained. No cyclisation occurred (cf. ref. 15). $\lambda_{max.}$ 225, 294, 325, $\lambda_{min.}$ 217, 255, 298 mμ (log ε 4·02, 4·03, 4·30, 4·02, 3·19, and 4·01).

2-Ethoxycarbonyl-2-phenylazocyclopentanone.—The preceding experiment was repeated using 2-ethoxycarbonylcyclopentanone (17·1 g., 0·11 mole) in place of ethyl α-methylacetoacetate. The azo-ester was distilled, b. p. *ca.* 112°/10^{-3} mm. (slight decomp.). It formed an orange oil (17·6 g., 67·6%), n_D^{20} 1·5426 (Found: C, 65·1; H, 6·3; N, 10·9. Calc. for $C_{14}H_{16}N_2O_3$: C, 64·6; H, 6·2; N, 10·8%), $\nu_{max.}$ 1760, 1730 cm.$^{-1}$ (CO), no NH bands, $\lambda_{max.}$ 218, 275—277, 400, $\lambda_{min.}$ 237—238, 376 mμ (log ε 3·97, 3·97, 2·30, 3·51, and 2·29) [lit.,[4] n_D^{22} 1·5477, $\lambda_{max.}$ 270 (log ε 4·02)].

When 3-ethoxycarbonyl-1,6-dimethyl-2-piperidone was used instead of 2-ethoxycarbonylcyclopentanone, little or no coupling took place; only a small amount of tar was formed. The lactam also failed to couple with *p*-methoxybenzenediazonium chloride under these conditions. For the same coupling reaction under slightly alkaline conditions, see below.

*Ethyl α-(*p*-Methoxyphenylazo)-α-methylacetoacetate.*—*p*-Anisidine (299 g., 2·43 moles) was diazotised and coupled with ethyl α-methylacetoacetate (385 g., 1·1 × 2·43 moles) under the conditions already described. The mixture was adjusted to pH 5, stirred for 4 hr. at 0°, and then kept at 0° overnight. It was extracted with benzene and the benzene was washed with water and evaporated; the residual oil was degassed at 100°/0·1 mm., giving the *azo-ester* (593 g., 87·7%). It was entirely soluble in light petroleum. A portion was distilled, as a pale orange oil, b. p. 110—115°/10^{-4} mm., n_D^{20} 1·5418 (Found: C, 60·0; H, 6·6; N, 9·7. $C_{14}H_{18}N_2O_4$ requires C, 60·4; H, 6·5; N, 10·1%), $\nu_{max.}$ 1750, 1730 cm.$^{-1}$ (CO), no NH bands, $\lambda_{max.}$ 203·6, 233·2, 316·5, $\lambda_{min.}$ 213, 256·1 mμ (log ε 4·01, 4·05, 4·19, 3·83, and 3·35).

*Ethyl Pyruvate *p*-Methoxyphenylhydrazone.*—The azo-ester described above (0·85 g., 0·003 mole) was boiled with alcoholic phosphoric acid (3 ml.; 10% by volume) for ¼ hr. The hydrazone crystallised on cooling and was recrystallised from aqueous methanol, giving pale yellow

[20] L. Marion and C. W. Oldfield, *Canad. J. Res.*, 1947, **25**, 1.

[21] B. Robinson, *Chem. Rev.*, 1963, **63**, 373.

crystals, m. p. 94°. It was sparingly soluble in light petroleum (lit.,[10] m. p. 97°) (Found: N, 11·8. Calc. for $C_{12}H_{16}N_2O_3$: N, 11·9%), $\lambda_{max.}$ 202·8, 221·5, 306, 339, $\lambda_{min.}$ 260·8, 316·5 mμ (log ε 4·13, 4·04, 4·19, 4·27, 3·14, and 4·15).

Ethyl 5-Methoxyindole-2-carboxylate.—Ethyl α-(*p*-methoxyphenylazo)-α-methylacetoacetate (592 g., 2·13 moles) was added slowly with stirring to 3N-ethanolic hydrogen chloride (1620 ml.) preheated to 60—70°. An exothermic reaction started with formation of ammonium chloride and ethyl acetate; the rate of addition was such that a gentle reflux was maintained without external heating. Finally, the mixture was heated under reflux for 20 min. and cooled to 0° for 18 hr. The crude product was washed with ethanol and water and dried (307 g.). A further crop (20 g.) was obtained from the liquors. The indolic ester (327 g., 70·2%) had m. p. 154—157° (lit.,[9] 152°).

Cyclisation of the ethyl pyruvate *p*-methoxyphenylhydrazone gave an identical product. The ester (322 g., 1·47 moles) was converted into 5-methoxyindole by the procedure described below for 5-benzyloxy-7-methylindole. The product (154 g., 71%) had b. p. 100—110°/0·2 mm., m. p. 55—56° (lit.,[22] b. p. 123—125°/0·5 mm., m. p. 57—57·5°; lit.,[9] m. p. 53—54°).

Ethyl α-(p-Benzyloxyphenylazo)-α-methylacetoacetate.—*p*-Benzyloxyaniline (29·8 g., 0·15 mole) in warm ethanol (130 ml.) was treated with a mixture of concentrated hydrochloric acid (71·3 ml., 0·84 mole) and water (90 ml.), added all at one time to give a fine precipitate. This was cooled to 0° and diazotised with sodium nitrite (20·7 g., 2 × 0·15 mole) in water (42 ml.), and the clear solution was treated with urea (4·95 g., 1·1 × 0·075 mole) and sodium acetate (51·0 g., 0·37 mole). It was then coupled with an alkaline solution of ethyl α-methylacetoacetate (23·8 g., 1·1 × 0·15 mole) prepared under the general conditions given above. The mixture was adjusted to pH 4·5—5, stirred at 0° for 5 hr., and kept for 18 hr. at 10°. Extraction with benzene yielded an orange-yellow oil which was heated at 100°/0·1 mm. for 20 min., giving the *azo-ester* (49·7 g., 93·5%); it was soluble in warm light petroleum (Found: C, 67·9; H, 6·5; N, 7·9. $C_{20}H_{22}N_2O_4$ requires C, 67·8; H, 6·3; N, 7·9%), $\nu_{max.}$ 1750, 1730 cm.$^{-1}$ (CO), no NH bands, $\lambda_{max.}$ 314—315, $\lambda_{min.}$ 255 mμ (log ε 4·17 and 3·60). The ester could be distilled in small portions at 160°/10^{-3}—10^{-5} mm. with some decomposition. The spectra of the distillate were identical with those of crude material, but the microanalysis was less satisfactory.

Ethyl Pyruvate p-*Benzyloxyphenylhydrazone.*—The azo-ester (10·6 g., 0·03 mole) was refluxed for 15 min. with ethanolic phosphoric acid (30 ml.; 10% by volume) and cooled to 0°, giving the hydrazone (7·9 g., 84·3%); ethyl acetate was identified in the liquors. The hydrazone formed pale orange-yellowish crystals (from ethanol), m. p. 93—95° (Found: N, 9·0. Calc. for $C_{18}H_{20}N_2O_3$: N, 9·0%), $\lambda_{max.}$ 308, 339, $\lambda_{infl.}$ 220, 240, $\lambda_{min.}$ 265, 317 mμ (log ε 4·19, 4·29, 4·10, 4·03, 3·36, and 4·16) (lit.,[8] m. p. 97°).

Both the azo-ester and the hydrazone were cyclised by heating under reflux for ½ hr. with 3N-ethanolic hydrogen chloride (3 ml./1 g.), the yields of ethyl 5-benzyloxyindole-2-carboxylate being 72·5 and 81·5%, respectively.

2-Amino-5-benzyloxytoluene.—5-Benzyloxy-2-nitrotoluene [23] (146 g., 0·6 mole) suspended in methanol (292 ml.) was hydrogenated at 70°/75 atm. in the presence of Raney nickel W2 (10 ml. of settled catalyst) until 6 equivalents of hydrogen had been absorbed. After filtration and evaporation, the *base* was distilled, b. p. 141—143°/0·25 mm., n_D^{20} 1·605, m. p. *ca.* 28° (114 g., 89%). It darkened in air (Found: N, 6·3. $C_{14}H_{15}NO$ requires N, 6·6%). The *hydrochloride* had m. p. 223—224° (Found: Cl, 13·7. $C_{14}H_{15}NO,HCl$ requires Cl, 14·2%).

Ethyl α-(4-Benzyloxy-2-methylphenylazo)-α-methylacetoacetate.—2-Amino-5-benzyloxytoluene (113 g., 0·53 mole) was diazotised and coupled with ethyl α-methylacetoacetate as described for ethyl α-(*p*-benzyloxyphenylazo)-α-methylacetoacetate, to yield the *azo-ester* (185 g., 94·8%) as an orange-red oil, soluble in warm light petroleum. After heating for 20 min. at 100°/0·05 mm., it had n_D^{20} 1·5705, $\nu_{max.}$ 1745, 1720 cm.$^{-1}$ (CO), no NH bands, $\lambda_{max.}$ 322—323, $\lambda_{min.}$ 261 mμ (log ε 4·07 and 3·52) (Found: C, 68·55; H, 6·6; N, 7·5. $C_{21}H_{24}N_2O_4$ requires C, 68·5; H, 6·6; N, 7·6%). A portion was distilled in a molecular still (bath at 150°/10^{-5} mm.); the resulting yellow oil was identical (infrared spectrum) with the crude product, but the analysis was less satisfactory.

Ethyl Pyruvate 4-Benzyloxy-2-methylphenylhydrazone.—The azo-ester (1·58 g.) was heated under reflux for 15 min. with 10% ethanolic phosphoric acid (5 ml.). The *hydrazone* (0·7 g., 50%) crystallised on cooling. It formed pale yellow crystals (from ethanol), m. p. 72—74°

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[23] F. Bergel and A. L. Morrison, *J.*, 1943, 49.

(Found: C, 69·95; H, 6·75; N, 8·7. $C_{19}H_{22}N_2O_3$ requires C, 69·9; H, 6·8; N, 8·6%), $\lambda_{max.}$ 205, 241, 312, 368, $\lambda_{min.}$ 223, 272, 318 mμ (log ε 4·39, 4·02, 3·75, 4·22, 3·89, 3·23, and 3·73).

Ethyl 5-*Benzyloxy*-7-*methylindole*-2-*carboxylate*.—The azo-ester (180 g., 0·49 mole) was added to 3N-ethanolic hydrogen chloride (326 ml., 0·98 mole) and the solution was warmed until an exothermic reaction started. When this had ceased, the mixture was boiled for 15 min. and then partially evaporated and cooled, yielding the *ester* which was washed with alcohol and water and dried (43·7 g., 28·8%). After recrystallisation from carbon tetrachloride it formed needles, m. p. 136—137° (Found: N, 4·6. $C_{19}H_{19}NO_3$ requires N, 4·5%).

5-*Benzyloxy*-7-*methylindole*-2-*carboxylic acid*.—The above-described ester (43·6 g., 0·141 mole) was heated under reflux for 2 hr. with a solution of potassium hydroxide (27·8 g., 3 × 0·141 mole; 85% KOH) in water (350 ml.), after which the hot solution was diluted with an equal volume of water and acidified with hydrochloric acid. After keeping for 24 hr. at 0° the product was filtered off, washed thoroughly with water, and dried. The *acid* (35·2 g., 89%) crystallised from carbon tetrachloride, m. p. 152—153° (Found: N, 5·0. $C_{17}H_{15}NO_3$ requires N, 5·0%).

5-*Benzyloxy*-7-*methylindole*.—5-Benzyloxy-7-methylindole-2-carboxylic acid (34·1 g., 0·121 mole) was decarboxylated by dissolving in warm quinoline (97 ml.), adding copper chromite (0·4 g.), and boiling and stirring with nitrogen passing into the liquid. The reaction ceased after 1½—2 hr. The bulk of the quinoline was distilled *in vacuo* through a Vigreux column (b. p. 65°/0·1 mm.), and the residue, in ether, was washed with 2N-sodium hydroxide, 2N-hydrochloric acid, and water. The dried solution yielded the *indole* (16·5 g., 57·3%), which crystallised from benzene–light petroleum, m. p. 71—72° (Found: C, 81·1; H, 6·3; N, 5·95. $C_{16}H_{15}NO$ requires C, 81·0; H, 6·4; N, 5·9%).

Ethyl α-(p-*Chlorophenylazo*)-α-*methylacetoacetate*.—*p*-Chloroaniline (331 g., 2·6 moles) was diazotised and coupled with ethyl α-methylacetoacetate (412 g., 1·1 × 2·6 moles) according to the general procedure, the pH being adjusted to 5. A yellow oil formed which gradually turned to orange; later some solid began to form. The mixture was stirred for 18 hr. at 5—10°. The aqueous layer was then decanted and the combined oil and solid were filtered, the solid being washed with light petroleum containing 10% of benzene. After further washing with water, ethyl pyruvate *p*-chlorophenylhydrazone (83 g., 13·3%) was obtained, m. p. 136—137°. It was identical with material made by refluxing an ethanolic solution of pyruvic acid with *p*-chlorophenylhydrazine hydrochloride, $\lambda_{max.}$ 205·1, 241·3, 300·3, 329·5, $\lambda_{min.}$ 235·6, 260·4, 308 mμ (log ε 4·06, 3·84, 4·23, 4·34, 3·82, 3·18, and 4·20).

The oil, with the petrol–benzene washings, was washed with water, dried, and evaporated, finally at 100°/0·1 mm., and yielded the *azo-ester* (602 g., 82%). A portion was distilled as an orange-yellow oil, b. p. 90°/10^{-5} mm., n_D^{20} 1·5446 (Found: C, 55·3; H, 5·3; N, 10·0. $C_{13}H_{15}ClN_2O_3$ requires C, 55·2; H, 5·35; N, 9·9%). It was completely soluble in light petroleum, $\nu_{max.}$ 1750, 1730 cm.$^{-1}$ (CO), no NH bands, $\lambda_{max.}$ 203·6, 222·5, 284·5, 344·3, $\lambda_{min.}$ 209·3, 240·8, 333 mμ (log ε 4·01, 4·07, 4·10, 3·23, 3·91, 3·64, and 3·25).

Conversion of Ethyl α-(p-*Chlorophenylazo*)-α-*methylacetoacetate into Ethyl Pyruvate* p-*Chlorophenylhydrazone*.—The azo-ester (602 g., 2·13 moles) was dissolved in ethanol (600 ml.). After standing for 2 days the hydrazone (176 g.), m. p. 138°, was obtained. The filtrate was saturated with dry hydrogen chloride and boiled for 1 hr. After cooling, a further quantity of hydrazone was obtained. It was treated with boiling ethanol to separate an insoluble red by-product (18 g.), and then allowed to crystallise. The resulting hydrazone (243 g.) was identical with that obtained before the hydrogen chloride treatment. The grand total was thus 419 g. (81·6%). The red by-product had m. p. 242—244° (from dioxan); it was not identified (Found: C, 55·2; H, 3·5; Cl, 20·6; N, 16·2%).

Ethyl 5-*Chloroindole*-2-*carboxylate*.—Polyphosphoric acid (900 g.) was stirred at 120°, and ethyl pyruvate *p*-chlorophenylhydrazone (300 g., 1·25 mole) was added in portions (*ca.* 20 g.) at such a rate that the temperature was maintained at 120—140° without external heating. The mixture became very viscous. After completing the addition, heating was continued at 145° for 10 min. The mixture was cooled to 60° and cautiously treated with water (1·5 l.), after which the product was filtered off, washed, and dried. The crude indolic ester (280 g., 100%) had m. p. *ca.* 160° and was converted [11] directly into 5-chloroindole, m. p. 72—73° (75%).

Ethyl α-(2,4-*Dichlorophenylazo*)-α-*methylacetoacetate and Ethyl Pyruvate* 2,4-*Dichlorophenylhydrazone*.—2,4-Dichloroaniline (16·2 g., 0·1 mole) was diazotised and coupled with ethyl α-methylacetoacetate (15·8 g., 0·11 mole) under the general conditions. The mixture was adjusted to give a pH of about 5, and after a short time a yellow oily solid began to form; it was stirred at 0° for 5—6 hr., and left for 18 hr. at the same temperature. It was next extracted with benzene, and the extract was washed, dried, and evaporated to a small volume, giving the hydrazone (5 g.); further evaporation yielded the oily *azo-ester* (20 g.). The hydrazone crystallised from benzene–light petroleum, m. p. 119—120° (Found: Cl, 25·3; N, 10·2. Calc. for $C_{11}H_{12}Cl_2N_2O_2$: Cl, 25·8; N, 10·2%) (lit.,[13] m. p. 122·5°), $\lambda_{max.}$ 204, 300, 323, $\lambda_{min.}$ 258 and 309 mμ (log ε 4·25, 4·29, 4·28, 3·28, and 4·24). The azo-ester had b. p. 105°/10^{-4} mm. and formed an orange-yellow oil soluble in light petroleum (Found: C, 49·6; H, 4·7; Cl, 22·4. $C_{13}H_{14}Cl_2N_2O_3$ requires C, 49·2; H, 4·45; Cl, 22·4%), $\nu_{max.}$ 1755, 1730 cm.$^{-1}$ (CO), no NH bands, $\lambda_{max.}$ 231, 285, $\lambda_{min.}$ 222, 253·5 mμ (log ε 3·98, 4·01, 3·93, and 3·68).

Ethyl 5,7-*Dichloroindole*-2-*carboxylate*.—Polyphosphoric acid (10 g.) was heated to 70°, and the above-described hydrazone (5 g., 0·018 mole) was added with stirring. After a short time a vigorous exothermic reaction occurred and the temperature rose to 120°. The mixture was finally heated at 150—160° for 5 min., cooled, and treated with water and ether. The extract was filtered and the residue washed several times with more ether. Evaporation of the ether yielded the indolic ester which crystallised from ethanol in light yellow needles, m. p. 145° (2·35 g., 50%). Similar treatment of the oily residue (20 g.) from the Japp–Klingemann reaction yielded more of the ester (5·1 g.). Recrystallised ester melted at 152° (lit.,[13] 156—156·5°) (Found: Cl, 27·0; N, 5·6. Calc. for $C_{11}H_9Cl_2NO_2$: Cl, 27·45; N, 5·4%).

In another experiment the combined crude solid and oil from 2,4-dichloroaniline (0·266 mole) was cyclised in four 20-g. batches, and yielded the same ester (20·9 g., 30·5%).

5,7-*Dichloroindole*-2-*carboxylic Acid*.—The ethyl ester (29·0 g., 0·112 mole) was hydrolysed with potassium hydroxide (22·2 g., 3 × 0·112 mole) in water (250 ml., as described for 5-benzyloxy-7-methylindole-2-carboxylic acid. The acid (23 g., 89%) crystallised from ethanol, decomp. *ca.* 300° [lit.,[13] 312° (decomp.)] (Found: N, 6·0. Calc. for $C_9H_5Cl_2NO_2$: N, 6·1%).

5,7-*Dichloroindole*.—5,7-Dichloroindole-2-carboxylic acid (23 g., 0·1 mole) was decarboxylated in quinoline (100 ml.) in the presence of copper chromite (2 g.), as described for 5-benzyloxy-7-methylindole. The indole was purified by distillation, b. p. 85—90°/0·1 mm., m. p. 50° (11·6 g., 62·3%). Recrystallisation from light petroleum yielded crystals, m. p. 55° (lit.,[13] 58—58·5°) (Found: C, 52·3; H, 3·0. Calc. for $C_8H_5Cl_2N$: C, 51·7; H, 2·7%).

3-*Ethoxycarbonyl*-3-(p-*methoxyphenylazo*)-1,6-*dimethyl*-2-*piperidone*.—*p*-Anisidine (6·15 g., 0·05 mole) was diazotised as described above, except that no addition of sodium acetate was made. The solution was added to a solution of 3-ethoxycarbonyl-1,6-dimethyl-2-piperidone (9·96 g., 0·05 mole; for preparation see Part I [19]) in water (50 ml.), and saturated potassium carbonate solution was added until the pH was about 9. The solution was stirred at 0° for 12 hr., during which time a tarry product separated. A benzene extract of the tar was chromatographed on alumina and yielded 3 fractions: (a) eluted with benzene (2·5 g.), (b) eluted with benzene + 0·5% methanol (3·0 g.), (c) eluted with benzene + 1—2% methanol (0·5 g.). Fractions (a) and (c) crystallised readily and had m. p. 68—70° and *ca.* 180°, respectively; they were identical with the low- and high-melting isomers of 1,6-dimethylpiperidine-2,3-dione 3-*p*-methoxyphenylhydrazone obtained in Part I.[19]

Fraction (b) was distilled, b. p. *ca.* 160°/10^{-3} mm. (slight decomp.), and yielded the *azo-ester* as an orange gum which could not be solidified (Found: C, 62·2; H, 7·1; N, 13·2; O, 18·4. $C_{17}H_{23}N_3O_4$ requires C, 61·2; H, 7·0; N, 12·6; O, 19·2%), $\nu_{max.}$ (film) 1735, 1640 cm.$^{-1}$ (CO), no NH bands. In CCl_4 the band at 1640 cm.$^{-1}$ moved to 1660 cm.$^{-1}$, and a small band at 1685 cm.$^{-1}$ appeared. $\lambda_{max.}$ 226—230, 312, 362, $\lambda_{min.}$ 220, 264, 341 mμ (log ε 4·00, 4·03, 3·83, 3·98, 3·54, and 3·78).

Ethyl α-(o-*Tolylazo*)-α-*methylacetoacetate*.—*o*-Toluidine (53·5 ml., 0·5 mole) was diazotised with concentrated hydrochloric acid (238 ml., 2·8 moles), water (300 ml.), and sodium nitrite (69 g., 1·0 mole). After the destruction of the excess nitrous acid with urea (16·5 g., 1·1 × 0·25 mole), the solution was buffered by the addition of crystalline sodium acetate (68 g., 0·5 mole) and poured into a solution of ethyl α-methylacetoacetate (79·3 g., 0·55 mole) in ice (1 kg.) and water (600 ml.) containing potassium hydroxide (85·5 g., 1·3 moles; *ca.* 85% KOH). The pH was adjusted to 5—6 and the mixture stirred at 0° for 3 hr. and allowed to stand overnight at 0°. The red oil was extracted into benzene and the extracts were dried and evaporated, to give the *azo-ester* (129·5 g., 99%). A portion was distilled, to give a pale orange oil, b. p. 105°/0·1 mm. (Found: C, 64·6; H, 7·0; N, 10·7. $C_{14}H_{18}N_2O_3$ requires C, 64·1; H, 6·9; N, 10·7%), $\lambda_{max.}$ 285, $\lambda_{min.}$ 245 mμ, and an undistilled residue which showed signs of decomposition.

Ethyl Pyruvate o-*Tolyhydrazone*.—The undistilled residue above (*ca.* 4 g.) crystallised on cooling, and was recrystallised from light petroleum (b. p. 40—60°), to give pale yellow needles, m. p. 74—76° (lit. 76—77°) of the α-form of the phenylhydrazone (cf. ref. 20 and ref. 3) (Found: C, 65·0; H, 7·4; N, 12·7. Calc. for $C_{12}H_{16}N_2O_2$: C, 65·5; H, 7·3; N, 12·7%), $\lambda_{max.}$ 229—230, 281—285 infl., 318, $\lambda_{min.}$ 258 mμ.

The azo-ester above (10·0 g.) was dissolved in ethanolic hydrogen chloride (3N; 30 ml.) and allowed to stand at room temperature overnight. The precipitated solid was collected, washed with water, and dried (6·01 g., 72%). Recrystallisation from light petroleum gave pale yellow needles, m. p. 58—60° (lit. 62°) of the β-form of the hydrazone (Found: C, 65·85; H, 7·4; N, 12·8), $\lambda_{max.}$ 236, 290—300infl., 350—351, $\lambda_{min.}$ 270 mμ.

Ethyl 7-*Methylindole*-2-*carboxylate* (cf. ref. 20).—A mixture of the β-hydrazone above (33·0 g., 0·15 mole) and polyphosphoric acid (60 g.) was stirred under nitrogen and heated gently with a luminous flame. The mixture became homogeneous, and when the internal temperature reached 120° an exothermic reaction began. This was checked by external cooling with an ice-bath so that the internal temperature remained between 140—160°. The reaction mixture was then allowed to cool to 80° and was treated with water (120 ml.). The cooled suspension was extracted with ethyl acetate, and the combined extracts were washed with sodium hydrogen carbonate solution and water, and dried. The residue from the dried extracts (21·75 g.) was distilled *in vacuo*, to give the ester (13·58 g., 44·6%), b. p. 128—130°/0·25 mm. A sample recrystallised from methanol gave rods, m. p. 127—129° (lit., 131°).

7-*Methylindole*.—Hydrolysis and decarboxylation of the above ester and subsequent batches under the conditions described in ref. 20 gave a distilled product (57·3 g.), b. p. 82°/0·4 mm., from which only 32 g. of crystalline 7-methylindole, m. p. 78—79° (lit. 85°), was obtained; picrate, m. p. 176° (lit. 177·5°). The non-crystalline residue was redistilled, and a middle fraction (b. p. 74°/0·15 mm.) examined (Found: C, 82·4; H, 6·9; N, 10·8. C_9H_9N requires C, 82·4; H, 6·9; N, 10·7); picrate, m. p. 187—189° (decomp.) (from benzene) (Found: C, 50·1; H, 3·5; N, 15·3. $C_{15}H_{12}N_4O_7$ requires C, 50·0; H, 3·3; N, 15·5%) (lit. m. p.s for methylindole picrates: 4-Me 194°; 5-Me, 161·5°; 6-Me, 161·5°; 7-Me, 177·5°). The infrared spectrum was identical with those of methylindoles, but gas chromatography showed the oil to be a mixture of some 7-methylindole with a larger quantity of another component which by comparison with authentic samples was shown to be either 4- or 5-methylindole. The melting point of the picrate shows it to be the former.

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