121. *Cyclic Keto-amines. Part IV.*[1] *The Synthesis and Reactions of 1 : 2 : 3 : 4-Tetrahydro-2-methyl-4-oxo*iso*quinoline.*

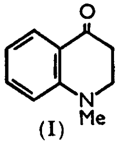
By I. G. Hinton and Frederick G. Mann.

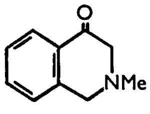
The above *iso*quinoline has been synthesised in order to investigate the chemistry of this novel type of *iso*quinoline derivative, and to compare it with that of the isomeric tetrahydro-1-methyl-4-oxoquinoline. The condensation product of ethyl *o*-chloromethylbenzoate and the ethyl ester of sarcosine has been subjected to a Dieckmann cyclisation, giving 3-ethoxycarbonyltetrahydro-2-methyl-4-oxo*iso*quinoline, which with hot acid underwent hydrolysis and decarboxylation to give the required oxo*iso*quinoline.

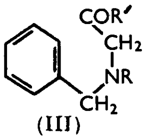
Salts of the oxo*iso*quinoline are stable, but the liquid base is readily oxidised by the air, ultimately to *N*-methylphthalimide. The base and its salts in solution undergo dehydrogenation even at room temperature, to give the 4-hydroxy-2-methyl*iso*quinolinium cation. This strong tendency to aromatise the heterocyclic ring is also shown by salts of the phenylhydrazone of the oxo*iso*quinoline, which readily undergo dismutation in acid solution to the corresponding salts of the 4-amino-2-methyl*iso*quinolinium cation and aniline. The semicarbazone similarly gives the same cation.

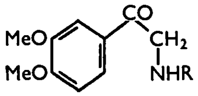
Other reactions of the oxo*iso*quinoline and of its 3-ethoxycarbonyl derivative are discussed.

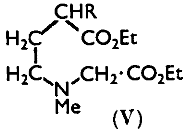
The synthesis and reactions of 1 : 2 : 3 : 4-tetrahydro-1-methyl-4-oxoquinoline (I) and its 1-phenyl analogue have been extensively investigated,[2] and we have extended these studies to the reactions of 1 : 2 : 3 : 4-tetrahydro-2-methyl-4-oxo*iso*quinoline (II). Previous attempts to synthesise compounds of type (II) have failed: for example, the cyclisation of the hydrochloride of *N*-benzyl-*N*-methylglycyl chloride[3] (III; R = Me, R′ = Cl) with aluminium chloride, or of *N*-benzyl-*N*-toluene-*p*-sulphonylglycine[4] (III; R = $SO_2{\cdot}C_6H_4Me$, R′ = OH) with phosphoric anhydride, failed. Attempted Bischler–Napieralski cyclisation of compounds such as *N*-(phenylacetyl)phenacylamine,[5] Ph·CO·CH_2·NH·CO·CH_2Ph, with phosphorus oxychloride gave oxazoles; and cyclisation of 3 : 4-dimethoxyphenacylamine (IV; R = H) with formaldehyde or of the *N*-formyl derivative (IV; R = ·CHO) with phosphorus oxychloride also failed.[6] The action of primary amines on *o*-chloromethylphenacyl chloride, Cl·CH_2·C_6H_4·CO·CH_2Cl, gave *iso*indolines (see following paper).

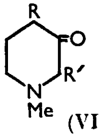

(I)


(II)


(III)


(IV)


(V)


(VI)

---

[1] Part III, Ittyerah and Mann, *J.*, 1958, 467.

[2] R. C. Cookson and Mann, *J.*, 1949, 67; Mann, *J.*, 1949, 2816; Allison, Braunholtz, and Mann, *J.*, 1954, 403; Braunholtz and Mann, *J.*, 1955, 381; 1957, 4166; 1958, 3368; cf. also ref. 1.

[3] Mannich and Kuphal, *Ber.*, 1912, **45**, 314.

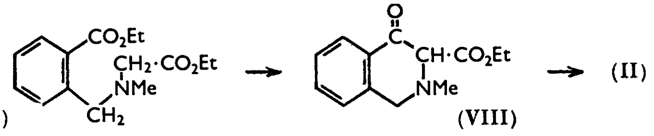
[4] Clemo and Perkin, *J.*, 1925, **127**, 2297.

[5] Robinson, *J.*, 1909, **95**, 2167; Young and Robinson, *J.*, 1933, 275.

[6] Campbell, Haworth, and Perkin, *J.*, 1926, 32.

McElvain *et al.*[7] have shown, however, that the ethyl ester of *N*-(3-ethoxycarbonylpropyl)sarcosine (V; R = H) is cyclised by sodium ethoxide in benzene to 2-ethoxycarbonyl-1-methyl-3-piperidone (VI; R = H, R′ = CO_2Et), which on acid hydrolysis furnishes 1-methyl-3-piperidone (VI; R = R′ = H); the 3-phenyl ester (V; R = Ph) reacted similarly with sodium hydride, and the product on hydrolysis afforded 1-methyl-4-phenyl-3-piperidone (VI; R = Ph, R′ = H). These 3-piperidones are readily oxidised, even by air at room temperature: they form stable hydrochlorides, but very unstable quaternary salts.

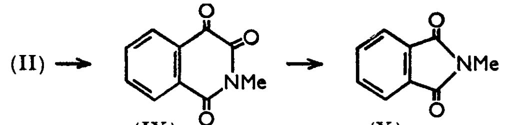
We have similarly condensed ethyl *o*-chloromethylbenzoate with the ethyl ester of sarcosine to give the ethyl ester of *N*-(*o*-ethoxycarbonylbenzyl)sarcosine (VII). The latter, when treated either with sodium ethoxide in boiling benzene or with sodium in boiling xylene, underwent cyclisation to give 3-ethoxycarbonyl-1 : 2 : 3 : 4-tetrahydro-2-methyl-4-oxo*iso*quinoline (VIII), a pale yellow liquid which darkened in air and in methanol gave a purple colour with ferric chloride. The ester (VIII) in boiling 18% hydrochloric acid underwent hydrolysis and decarboxylation, furnishing the hydrochloride of the tetrahydro-2-methyl-4-oxo*iso*quinoline (II) in 31% yield, based on the *o*-chloromethylbenzoate used. The pure base (II), like the ester (VIII), is also a pale yellow oil which darkens in air: it forms a stable colourless hydrochloride and methiodide, which readily recrystallise. The infrared spectrum of the base (II) shows the $>C{:}O$ band at 1690 and the =NMe band at 2755 cm.$^{-1}$; that of the hydrochloride shows the $>C{:}O$ band at 1692 and the $\equiv NH^+$ band at 2420 cm.$^{-1}$



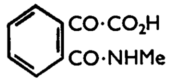
(VII) (VIII)

In view of the novel nature of the keto-amine (II), its reactions with various reagents are now recorded, with the exception of the series of compounds which can be obtained initially by condensation of the keto-amine (II) with *o*-aminobenzaldehyde: these compounds will be described later.

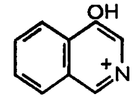
The oxo*iso*quinoline (II), when heated in dichromic–sulphuric acid solution, is oxidised to 1 : 2 : 3 : 4-tetrahydro-2-methyl-1 : 3 : 4-trioxo*iso*quinoline (IX): when air is bubbled through a suspension of the base (II) in aqueous sodium hydroxide even at room temperature, oxidation with ring contraction occurs to form *N*-methylphthalimide (X). It is probable that this oxidation proceeds through the trioxo-compound (IX), for Freund and Beck[8] have shown that 1 : 2 : 3 : 4-tetrahydro-2-methyl*iso*quinoline is also oxidised by dichromic acid to the trioxo-compound (IX), which with alkaline permanganate readily gives the phthalimide (X). Elderfield[9] has suggested that the last stage in this process, namely, (IX) ⟶ (X), involves the intermediate formation of the amide (XI).



(IX) (X)



(XI)



(XII)

The oxo*iso*quinoline (II) in aqueous-alkaline suspension is dehydrogenated at room temperature even by cupric chloride to form the 4-hydroxy-2-methyl*iso*quinolinium cation, isolated as the picrate (XII; X = $\cdot O\cdot C_6H_2O_6N_3$). Bromine in cold carbon tetrachloride similarly converts the free base (II) into the bromide (XII; X = Br): the use of

---

[7] Prill and McElvain, *J. Amer. Chem. Soc.*, 1933, **55**, 1236; McElvain and Laughton, *ibid.*, 1951, **73**, 448.

[8] Freund and Beck, *Ber.*, 1904, **37**, 1945.

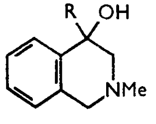
[9] Elderfield, " Heterocyclic Compounds," Wiley, New York, 1952, Vol. IV, p. 405.

an excess of bromine, with subsequent warming, furnished in addition the trioxo-compound (IX) in small yield.

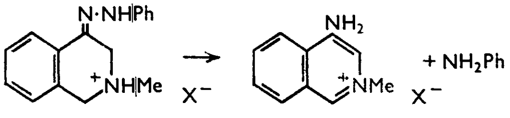
Aqueous bromine, and *N*-bromosuccinimide in carbon tetrachloride, apparently cause complex reactions, and from the products only the hydrobromide of the base (II) has been isolated.

The keto-group in the base (II) behaves normally with lithium aluminium hydride and with phenylmagnesium bromide, giving tetrahydro-4-hydroxy-2-methyl*iso*quinoline (XIII; R = H) and its 4-phenyl derivative (XIII; R = Ph) respectively. The latter on dehydration affords 1 : 2-dihydro-2-methyl-4-phenyl*iso*quinoline.

Condensation of the keto-group in the base (II) with phenylhydrazine and similar compounds reveals a striking reaction. A cold ethanolic solution of the hydrochloride of the base (II), when treated with 1·5 equivalents of phenylhydrazine, slowly deposits the white crystalline phenylhydrazone hydrochloride (XIV; X = Cl): this salt is stable to aerial oxidation and can be readily converted into a number of analogous stable salts. The white free phenylhydrazone can be obtained by the action of aqueous alkali on the hydrochloride in nitrogen: it is, however, highly unstable in the presence of air, forming a red viscous syrup from which no definite product could be isolated. The salts of the phenylhydrazone readily undergo a dismutation to equivalent quantities of the corresponding salt of the 4-amino-2-methyl*iso*quinolinium cation (XV) and aniline. The hydrochloride (XIV; X = Cl), for example, undergoes this change on attempted sublimation, and also rapidly when heated with ethanolic hydrogen chloride, dilute sulphuric acid, or glacial acetic acid. This ready reaction prevents therefore the successful application of the Fischer indolisation reaction, which requires an acidic medium.



(XIII)



(XIV) (XV)

The 2 : 4-dinitrophenylhydrazone and the semicarbazone of the base (II) also give the cation (XV) in the presence of warm acids, and the reaction affords another notable example of the readiness with which the heterocyclic ring in the base (II) and its derivatives undergoes aromatisation.

An ethanolic solution of the base (II) containing sodium acetate and a considerable excess of phenylhydrazine, when boiled for one day in air, deposited deep orange crystals, of empirical formula $C_{22}H_{17}N_5$. The infrared spectrum of this product showed the absence of an $>$NH group. The low solubility made reliable molecular-weight determinations difficult, and its structure has not been elucidated.

The hydrochloride of the base (II) did not react with hydrazine, or undergo the Mannich reaction with dimethylamine and formaldehyde. It is noteworthy that the isomeric base (I) gave the Mannich reaction, but the product spontaneously decomposed to form the 3-methylene derivative, which isomerised to the very stable 1 : 4-dihydro-1 : 3-dimethyl-4-oxoquinoline[10] (XVI): a similar series of reactions, involving an analogous migration of a hydrogen atom, is clearly not possible with the base (II). Furthermore, the base (II), unlike its isomer (I), did not react with malononitrile under the usual conditions,[11] and it did not form a cyanohydrin.

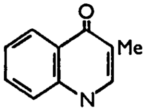
The reactivity of the 3-methylene group in the base (II) is shown by the action of benzaldehyde, which gives an unstable pale yellow 3-benzylidene derivative, and of *p*-dimethylaminobenzaldehyde, which gives the stable orange 3-(*p*-dimethylaminobenzylidene) derivative (XVII). The colour and stability of this compound indicate a contributory

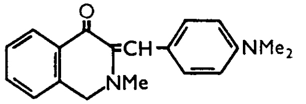
---

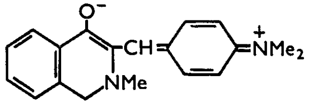
[10] Ittyerah and Mann, *J.*, 1958, 467.

[11] McElvain and Lyle, *J. Amer. Chem. Soc.*, 1950, **72**, 384; Ittyerah and Mann, *J.*, 1956, 3179.

polar form (XVIIB), and this is confirmed by the formation of a colourless diperchlorate: the compound is in fact a *mero*cyanine. The base (II) also reacted with *p*-nitrosodimethylaniline to form a deep red 3-(*p*-dimethylaminophenylimino)-derivative, which was too unstable to allow isolation in the pure state. Spectroscopic examination of the corresponding derivative from the base (I) had shown that a hydrogen atom had migrated from


(XVI)

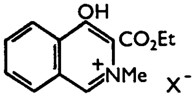

(XVIIA)

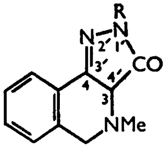

(XVIIB)

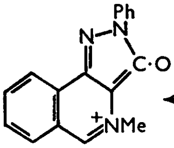
the 2-position to the imino-nitrogen atom, and that the compound was therefore the isomeric 3-(*p*-dimethylaminoanilino)-derivative, having the stable heterocyclic ring of the compound (XVI): this stabilising isomeric change is again impossible in our *iso*quinoline analogue.

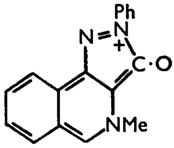
Attempted condensation of the keto-amine (II) with various diazo-salts in aqueous sodium acetate solution did not succeed.

3-Ethoxycarbonyl-4-oxo*iso*quinoline (VIII) differed from the keto-amine (II) and from tetrahydro-2-methyl*iso*quinoline in that a hot sulphuric–dichromic acid solution oxidised it to *N*-methylphthalimide, and the intermediate trioxo-derivative (IX) was not isolated. It was also very readily dehydrogenated by cold aqueous cupric acetate with the formation of the 3-ethoxycarbonyl-4-hydroxy-2-methyl*iso*quinolinium cation (XVIII), which has been isolated as the perchlorate and picrate and with hot hydrochloric acid readily undergoes hydrolysis and decarboxylation to form the cation (XII), also isolated as the picrate.


(XVIII)


(XIX)


(XXA)


(XXB)

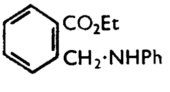
The 3-ethoxycarbonyl base (VII) in hot ethanolic solution reacted with hydrazine and with phenylhydrazine to give compounds whose analyses indicated the expected pyrazolino*iso*quinolines (XIX; R = H and Ph, respectively): the salts of the last compound also had the expected composition. The structure (XIX) must, however, at present be accepted with reserve. Both hydrazine derivatives are deep red and form pale yellow hydrochlorides, whereas compounds of structure (XIX) should be colourless: both derivatives, moreover, are appreciably soluble in water. If, however, the hydrazine had in each case dehydrogenated the pyrazoline (a process which has been recorded[12]), *mero*cyanines would have been produced, of which (XXA and B) are the two contributory polar forms of the 1′-phenyl derivative, and deep colour would be expected. Chemical analysis does not differentiate decisively between the forms (XIX) and (XXA–B), and the infrared and nuclear magnetic resonance spectra give inconclusive structural evidence.

The infrared spectrum of the 1′-phenyl compound in Nujol and in hexachlorobutadiene mulls shows a strong band at 1635 cm.$^{-1}$, which most probably indicates a strong conjugated or amide-type $>$C:O group: it could possibly indicate a $>$C:N– group in a conjugated system but its intensity is rather great for this assignment. The spectrum is virtually unchanged when a chloroform solution is employed. The nuclear magnetic resonance spectrum shows a strong sharp band at 1·10, which could represent a methyl group of the type $Me{\cdot}N^{+}\equiv$ or $Me{\cdot}N(-C=C-)_2$, but not one of the normal $Me{\cdot}N=$ type, which

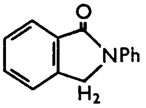
---

[12] Gardner, Haynes, and Brandon, *J. Org. Chem.*, 1957, **22**, 1206.

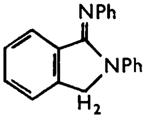
should have $\sigma \sim 2{\cdot}0$—$2{\cdot}5$. The infrared spectrum of the hydrochloride of the 1′-phenyl compound shows a broad band at 2610 cm.$^{-1}$, probably indicating a $\equiv NH^+$ group (although it might indicate a strongly hydrogen-bonded OH group), and a strong band at 1674 cm.$^{-1}$, which suggests a normal conjugated $\gt C{:}O$ group: the change in position of this band on salt formation is striking. These results do not afford strong support for the structure (XIX) or (XXA–B), or for that expected for their salts.



(XXI)



(XXII)

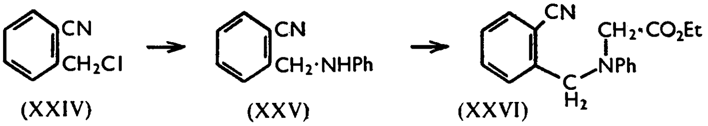


(XXIII)

It is noteworthy that the infrared spectrum of the simpler 1 : 3-diphenylpyrazol-5-one in the above mulls shows no $\gt C{:}O$ absorption, but has a broad band centred at *ca.* 2500 cm.$^{-1}$ which might indicate a $\equiv NH^+$ group or a strongly hydrogen-bonded OH group.

The synthesis of 1 : 2 : 3 : 4-tetrahydro-4-oxo-2-phenyl*iso*quinoline has been briefly investigated. The *N*-phenyl analogue of the *N*-methyl-diester (VII) could not be prepared, for the ethyl ester of *N*-phenylglycine did not condense with ethyl *o*-chloromethyl- or *o*-bromomethyl-benzoate. The alternative intermediate (XXI) could not be prepared by interaction of ethyl *o*-chloromethylbenzoate and aniline (2 equivalents), for these compounds at room temperature readily gave 1-oxo-2-phenyl*iso*indoline (XXII).

o-Chloromethylbenzonitrile (XXIV) with aniline at 100° in the absence of a solvent gave 2-phenyl-1-phenylimino*iso*indoline (XXIII) in low yield, but in boiling ethanol furnished *N*-2-cyanobenzylaniline (XXV). This compound in turn with ethyl bromoacetate gave the ethyl ester of *N*-2-cyanobenzyl-*N*-phenylglycine (XXVI) but only in very low yield.



(XXIV) (XXV) (XXVI)

This nitrile-ester when treated in boiling xylene with sodium gave only a tar, and in boiling ethanol with sodium ethoxide gave 1-oxo-2-phenyl*iso*indoline (XXII). The failure to achieve this cyclisation was not unexpected, as it would have involved a mechanism essentially different from that of the cyclisation of the diester (VII).

EXPERIMENTAL

Consistent m. p.s of certain compounds could be obtained only by the use of evacuated capillary tubes, noted as (E.T.): the temperature of immersion, if above room temperature, is denoted as (T.I.).

Ethyl o-*Chloromethylbenzoate.*—Chlorine was bubbled through *o*-toluoyl chloride at 185—200° until the increase in weight was 90% (not more!) of that required for monochlorination. Fractional distillation gave *o*-chloromethylbenzoyl chloride, b. p. 135°/14 mm. (lit.,[13] 129—133°/12 mm.), in almost theoretical yield, allowing for recovered *o*-toluoyl chloride, b. p. 108°/14 mm. A solution of the benzoyl chloride in a large excess of ethanol was set aside for 24 hr. and then evaporated under reduced pressure: the residue on distillation gave the chloromethylbenzoate, b. p. 140°/14 mm. (lit.,[13] 139—143°/12 mm.) in almost theoretical yield.

Ethyl *o*-bromomethylbenzoate was prepared by the method of Davies and Perkin; [14] it was used without distillation since when heated it readily gave phthalide. In later experiments it was replaced by the chloro-derivative.

---

[13] Morgan and Porter, *J.*, 1926, 1262.

[14] Davies and Perkin, *J.*, 1922, **121**, 2207.

Ethyl Ester of Sarcosine.—Sarcosine nitrile, b. p. 96°/1 mm., was prepared in 70% yield from methylamine hydrochloride by Staudt's method:[15] it gave a picrate, needles, m. p. 147—148° (lit.,[16] 142—143°) from ethanol (Found: C, 38·4; H, 4·1. Calc. for $C_3H_6N_2,C_6H_3O_7N_3$: C, 38·1; H, 4·0%). Its conversion into the ester is much improved as follows: Dry hydrogen chloride was passed slowly into a cold solution of the nitrile (200 g.) in absolute ethanol (2 l.) under reflux, the heat of the reaction eventually boiling the solution, which was then cooled, resaturated with the chloride, and heated under reflux for 8 hr. The cold solution, filtered to remove ammonium chloride, was evaporated under reduced pressure. The crude crushed residual sarcosine ester hydrochloride was added to an excess of liquid ammonia, which was then allowed to evaporate. An ethereal extract of the residue, when dried (Na_2SO_4) and distilled, gave the ester (135 g., 40%), b. p. 46—51°/13 mm. (lit.,[16] 52°/15 mm.). The use of chilled 10% aqueous sodium hydroxide in place of the ammonia gave inconsistent yields, never above 28%.

The base (II) is best prepared and stored as its stable hydrochloride without purification of the intermediate compounds. The isolation and identification of these compounds are briefly noted.

Ethyl Ester of N-(o-*Ethoxycarbonylbenzyl*)*sarcosine* (VII).—A solution of the ethyl ester of sarcosine (109 g., 2 mols.) in ether (100 c.c.) was added slowly to an ice-cooled solution of ethyl *o*-chloromethylbenzoate (92 g., 1 mol.) in ether (100 c.c.) which was then set aside at room temperature for 24 hr. The ether was distilled, and the residue extracted with water (to remove sarcosine ester hydrochloride) and with ether. The ethereal extract was dried (Na_2SO_4), and on evaporation left the diester (VII) (136 g., almost 100%). A sample on distillation gave the pure *diester* (VII), b. p. 182—183°/10 mm. (Found: C, 64·6; H, 8·0; N, 5·3. $C_{15}H_{21}O_4N$ requires C, 64·5; H, 7·5; N, 5·0%). The use of ethyl *o*-bromomethylbenzoate gave a product requiring extensive fractionation.

The diester gave a *chloroplatinate* as a buff powder, m. p. 204·5° (decomp.) (Found: C, 37·6; H, 4·7. $2C_{15}H_{21}O_4N,H_2PtCl_6$ requires C, 37·3; H, 4·4%).

3-*Ethoxycarbonyl*-1 : 2 : 3 : 4-*tetrahydro*-2-*methyl*-4-*oxo*iso*quinoline* (VIII).—A mixture of the diester (VII) (45 g.), sodium ethoxide (15 g., 1·3 mols.), and benzene (100 c.c.) was heated under a reflux air-condenser carrying a stillhead and receiver, so that an azeotropic ethanol–benzene fraction slowly distilled (*ca.* 4 hr.). The cold mixture was shaken with water, to which concentrated hydrochloric acid was added until the mixture was just acid to Congo Red. An excess of sodium hydrogen carbonate was added, and the benzene layer when dried (Na_2SO_4) and distilled gave the yellow oily *ester* (VIII), b. p. 130°/0·65 mm. (Found: C, 66·0; H, 6·7; N, 6·0%; *M*, in freezing benzene, 210. $C_{13}H_{15}O_3N$ requires C, 66·9; H, 6·5; N, 6·0%; *M*, 233). It gave a yellow crystalline *picrate*, m. p. 128—129° (from ethanol) (Found: C, 49·6; H, 3·8; N, 12·2. $C_{13}H_{15}O_3N,C_6H_3O_7N_3$ requires C, 49·4; H, 3·9; N, 12·1%), and an orange *chloroplatinate*, m. p. 176—177°, precipitated from an ethanolic solution of the ester (Found: C, 37·7; H, 4·5. $2C_{13}H_{15}O_3N,H_2PtCl_6,2C_2H_6O$ requires C, 37·2; H, 4·6%). Dry hydrogen chloride, when passed into an ethereal solution of the ester, deposited the hygroscopic white hydrochloride, m. p. 137°; an ethanolic solution similarly deposited the white hydrobromide, m. p. 172°.

Tetrahydro-2-*methyl*-4-*oxo*iso*quinoline* (II).—The undistilled diester (VII) (136 g.), prepared as described above, was added to " molecular " sodium in xylene [sodium (12 g.) and xylene (250 c.c.)], which was vigorously stirred under nitrogen whilst heated under reflux for 8 hr. The cold dark brown product was extracted with dilute hydrochloric acid, which was filtered and treated with sodium hydrogen carbonate in excess, the liberated ester (VIII) being then extracted with ether. The ether was in turn extracted with 18% hydrochloric acid (400 c.c.), which was boiled under reflux for 12 hr., charcoal (1 g.) being added after the first 4 hr. The hot filtered solution was evaporated to dryness under reduced pressure. The brown crystalline residue, when washed with boiling ethanol (2 × 200 c.c.) and dried, afforded the pure colourless *hydrochloride* of the base (II), m. p. 250° (sealed tube) (24 g., 31%) (Found: C, 60·8; H, 6·1; N, 7·0. $C_{10}H_{11}ON,HCl$ requires C, 60·7; H, 6·1; N, 7·1%). The consistently high yields obtained by this method depend largely on the fact that distillation of the intermediate esters (VII) and (VIII) is avoided.

The *base* (II), when liberated from the hydrochloride, extracted with ether, dried, and

---

[15] Staudt, *Z. physiol. Chem.*, 1925, **146**, 286.

[16] Dalgliesh and Mann, *J.*, 1947, 658.

distilled in nitrogen, formed a pale yellow oil, b. p. 81—83°/0·4 mm. (Found: C, 73·4; H, 6·7; N, 8·6. $C_{10}H_{11}ON$ requires C, 74·5; H, 6·8; N, 8·7%).

Addition of concentrated hydrobromic acid to the ethanolic base precipitated the colourless *hydrobromide*, m. p. 242—244° (decomp.) (from 96% ethanol) (Found: C, 49·7; H, 5·1; N, 5·7. $C_{10}H_{11}ON,HBr$ requires C, 49·6; H, 5·0; N, 5·8%). The colourless *perchlorate*, similarly prepared and recrystallised, had m. p. 159—164° (T.I. 120°) (Found: C, 45·5; H, 4·9; N, 5·4. $C_{10}H_{11}ON,HClO_4$ requires C, 45·9; H, 4·6; N, 5·4%). The base gave a *picrate*, m. p. 133° (decomp., T.I. 127°) (from ethanol) (Found: C, 49·2; H, 3·4; N, 14·7. $C_{10}H_{11}ON,C_6H_3O_7N_3$ requires C, 49·2; H, 3·6; N, 14·3%). This picrate, when subjected to repeated crystallisation from ethanol in the presence of air underwent dehydrogenation, with conversion into *4-hydroxy-2-methyl*iso*quinolinium picrate* (XII; $X = C_6H_2O_7N_3$), m. p. and mixed m. p. 227° (see below) (Found: C, 49·5; H, 3·4; N, 14·0. $C_{16}H_{12}O_8N_4$ requires C, 49·5; H, 3·1; N, 14·4%).

A solution of the base (II) in methyl iodide, when boiled for 1 hr. and evaporated, gave the methiodide, m. p. 196—197° (from methanol): this salt gave the yellow crystalline *methopicrate*, m. p. 207—208° (from methanol) (Found: C, 51·1; H, 4·1; N, 14·0. $C_{17}H_{16}O_8N_4$ requires C, 50·9; H, 4·0; N, 13·9%).

Oxidation of the Base (II).—(*A*) Sodium dichromate (2 g.) was added to a solution of the keto-amine hydrochloride (0·5 g.) in water (5 c.c.) and sulphuric acid (18 c.c.), which was then boiled for 30 min., white needles separating meanwhile. The needles, when collected from the cold mixture, washed with water, and dried, afforded tetrahydro-2-methyl-1 : 3 : 4-trioxo*iso*quinoline (IX) (0·35 g., 75%), m. p. 186—188° (lit.,[8] 186—187°) (from ethanol) (Found: C, 63·4; H, 3·5. Calc. for $C_{10}H_7O_3N$: C, 63·5; H, 3·7%).

(*B*) A fine jet of air was blown through the suspension of the base (II) prepared by the addition of the keto-amine hydrochloride (1 g.) in water (5 c.c.) to 10% aqueous sodium hydroxide (50 c.c.). The colour deepened and the suspension slowly formed a dark brown tar. After 45 min., ether (10 c.c.) was added to dissolve much of the tar, and the air-current then deposited a trace of brown powder. The filtered solution was extracted with ether (7 × 250 c.c.), and the extract dried (Na_2SO_4) and evaporated. The residual dark yellow oil, when rubbed in turn with ethanol and light petroleum (b. p. 40—60°), afforded crystalline *N*-methylphthalimide, needles, m. p. 129° (lit.,[8] 133—134°) after sublimation at 130°/0·0001 mm. It was identified by its infrared spectrum, which showed bands at 1755 and 1722 cm.$^{-1}$, characteristic of the phthalimide ring.

Dehydrogenation of the Base (II).—(*A*) 5% Aqueous sodium hydroxide (2 c.c., 1 mol.) was added to a solution of the keto-amine hydrochloride (0·5 g., 1 mol.) and cupric chloride dihydrate (0·85 g., 2 mols.) in water (25 c.c.), which was set aside for 24 hr. The greyish-white precipitate, when recrystallised from dilute hydrochloric acid, gave a chlorocuprite of the cation (XII). This powdered salt, when added to hot aqueous sodium picrate, deposited 4-hydroxy-2-methyl*iso*quinolinium picrate (XII; $X = C_6H_2O_7N_3$), m. p., mixed and unmixed, 224—228° (E.T.) (from ethanol).

(*B*) Bromine (0·25 g.) in carbon tetrachloride (10 c.c.) was added dropwise with shaking to the free base (0·25 g., 1 mol.) in carbon tetrachloride (10 c.c.). The clear colourless solution was decanted from the precipitated yellowish gum, a solution of which in ethanol was then boiled (charcoal), filtered, cooled, and diluted with ether. The crystalline bromide (XII; X = Br), m. p. 224—230° (E.T.), which separated could not be readily recrystallised and was therefore converted into the picrate (XII; $X = C_6H_2O_7N_3$), m. p. and mixed m. p. 222—226° (E.T.).

When an excess of bromine was used and the mixture then evaporated to dryness, the residue when heated at 135°/0·0001 mm. gave a small sublimate of the trioxo*iso*quinoline (IX), m. p. 185—186° (mixed m. p. 184—187°) after crystallisation from ethanol. The unsublimed residue, m. p. 233°, was almost certainly the bromide (XII; X = Br).

N-Bromosuccinimide (0·3 g.) and benzoyl peroxide (trace) were added to a stirred solution of the base (II) (0·25 g.) in carbon tetrachloride (7 c.c.) under nitrogen, giving an immediate yellow precipitate. After 6 hr., the orange deposit was collected and thrice recrystallised from ethanol giving the hydrobromide of the base (II), m. p. 239—240° (decomp.) (E.T., T.I. 195°), mixed m. p. 240—242° (Found: C, 49·4; H, 4·9; N, 5·7%), which gave the picrate of the base, m. p. and mixed m. p. 132—133° (T.I. 120°). The hydrobromide is almost certainly formed by the interaction of the orange solid and the hot solvent.

Reduction of the Base (II).—An ethereal solution of the base was added to an excess of lithium aluminium hydride in ether, which boiled spontaneously during the addition. The mixture was set aside for 12 hr., the excess of hydride destroyed by dilute sulphuric acid, and the mixture neutralised with sodium carbonate and extracted with ether. Evaporation of the dried extract afforded crude 1 : 2 : 3 : 4-tetrahydro-4-hydroxy-2-methyl*iso*quinoline (XIII; R = H) as a brown oil, which gave a yellow *picrate*, m. p. 149—150° (from ethanol) (Found: C, 49·4; H, 4·6; N, 14·2. $C_{10}H_{13}ON,C_6H_3O_7N_3$ requires C, 49·0; H, 4·1; N, 14·3%).

An ethereal solution of phenylmagnesium bromide was added with stirring to a similar solution of the base (II), under nitrogen. After 15 min., the mixture was hydrolysed with dilute hydrochloric acid, and the aqueous layer separated, neutralised with sodium carbonate, and extracted with ether. Evaporation gave *tetrahydro-4-hydroxy-2-methyl-4-phenyl*iso*quinoline* (XIII; R = Ph), m. p. 107·5—108·5° (from ethanol) (Found: C, 80·2; H, 7·1; N, 5·8. $C_{16}H_{17}ON$ requires C, 80·3; H, 7·2; N, 5·9%). Hydrogen chloride, when passed into an ethanolic solution, gave the colourless *hydrochloride*, m. p. 219° (T.I. 206°) (from ethanol) (Found: C, 69·8; H, 6·6. $C_{16}H_{17}ON,HCl$ requires C, 69·7; H, 6·6%). The yellow *picrate* had m. p. 179° (decomp.) (from ethanol) (Found: C, 56·2; H, 4·1; N, 12·1. $C_{16}H_{17}ON,C_6H_3O_7N_3$ requires C, 56·4; H, 4·3; N, 12·0%).

A solution of this base (XIII; R = Ph) (0·18 g.) in acetic acid (3 c.c.) and 48% hydrobromic acid (1 c.c.) was boiled under reflux for 15 min., concentrated, and treated with aqueous sodium carbonate, the precipitated colourless syrup being extracted with ether. Evaporation of the extract afforded 1 : 2-dihydro-2-methyl-4-phenyl*iso*quinoline as oily crystals, which gave a yellow *picrate*, m. p. 203—204° (T.I. 100°) after repeated crystallisation from ethanol (Found: C, 58·5; H, 3·9. $C_{16}H_{15}N,C_6H_3O_7N_3$ requires C, 58·6; H, 4·0%).

Action of Phenylhydrazine.—The keto-amine hydrochloride (1 g.) and pure phenylhydrazine (0·75 g., 1·5 mol.) were added to cold ethanol (20 c.c.) under nitrogen. The hydrochloride dissolved within 5 min. and the clear solution soon deposited the *phenylhydrazone hydrochloride* (XIV; X = Cl) as very fine white crystals. The mixture was set aside for 48 hr. to increase the size of the crystals (1·5 g., yield almost theoretical), which when collected and recrystallised from ethanol melted at 190° (effervescence), immediately resolidified, and remelted at *ca.* 260° (Found: C, 66·5; H, 6·2; N, 14·4. $C_{16}H_{17}N_3,HCl$ requires C, 66·8; H, 6·3; N, 14·6%).

The above hydrochloride was added under nitrogen to a mixture of 10% aqueous sodium hydroxide and ether, which was shaken for 30 min. The ether layer was dried ($MgSO_4$) and evaporated, and the residue recrystallised four times from ethanol under nitrogen, affording the colourless *phenylhydrazone*, m. p. 110—119° (slow decomp.) (Found: C, 76·2; H, 7·4; N, 16·6. $C_{16}H_{17}N_3$ requires C, 76·5; H, 6·8; N, 16·7%). The phenylhydrazone was also obtained less expeditiously by the action of phenylhydrazine (1 mol.) on the base (II) in boiling ethanol containing sodium acetate, under nitrogen.

The following salts were obtained by precipitation from an ethanolic solution of the hydrochloride: *picrate* (XIV; X = $C_6H_2O_7N_3$), yellow, m. p. 173° (decomp.) (T.I. 170°) (from ethanol) (Found: C, 54·7; H, 4·7; N, 17·7. $C_{16}H_{17}N_3,C_6H_3O_7N_3$ requires C, 54·7; H, 4·7; N, 17·7%); *perchlorate* (XIV; X = ClO_4), colourless, m. p. 164° (from ethanol) (Found: C, 54·5; H, 4·9; N, 12·2. $C_{16}H_{17}N_3,HClO_4$ requires C, 54·6; H, 5·2; N, 12·0%); *chloroplatinate*, purple-brown, m. p. 164° (decomp.) after thorough washing with ethanol and drying at room temperature (Found: C, 42·7; H, 4·2; N, 9·6. $2C_{16}H_{17}N_3,H_2PtCl_6$ requires C, 42·1; H, 4·0; N, 9·2%).

A solution of the hydrochloride (5 g.) of the base (II), phenylhydrazine (10 g., 2·5 mol.) and sodium acetate (10 g.) in ethanol (50 c.c.) was boiled under reflux in air for 24 hr. and cooled. The solid deposit, when washed with water and ether, gave an orange residue (1·1 g.), which after two recrystallisations from ethanol (in which it was very slightly soluble) afforded orange needles, m. p. 213° (Found, in independent preparations: C, 75·2, 75·1, 75·4; H, 5·1, 5·1, 5·0; N, 20·1, 19·8, 20·1%; *M*, in boiling CCl_4, 300. $C_{22}H_{17}N_5$ requires C, 75·2; H, 4·9; N, 19·9%; *M*, 351). This compound was not obtained when the boiling was conducted in nitrogen.

Action of Acids on the Phenylhydrazone Hydrochloride (XIV; X = Cl).—(i) A solution of the hydrochloride in saturated ethanolic hydrogen chloride, when boiled under reflux for 2 hr. and cooled, deposited crude crystalline 4-amino-2-methyl*iso*quinolinium chloride (XV; X = Cl), which was converted into the yellow *picrate*, m. p. 220—221° (alone and mixed with the synthetic material described below) (from ethanol) (Found: C, 49·0; H, 3·6; N, 17·5. $C_{16}H_{13}O_7N_5$ requires C, 49·6; H, 3·4; N, 18·1%). The original reaction liquor was basified and extracted with ether, which when separated and evaporated afforded aniline, identified by (*a*) the purple coloration with sodium hypochlorite solution, (*b*) conversion into acetanilide, m. p. and mixed m. p. 110—114°.

(ii) The solution in a similar experiment in which 10% aqueous sulphuric acid was used deposited on cooling colourless needles of the *hydrogen sulphate* (XV; X = HSO_4), m. p. 225—227° after crystallisation from 97% ethanol (Found: C, 47·1; N, 5·0; N, 11·0. $C_{10}H_{12}O_4N_2S$ requires C, 46·9; H, 4·7; N, 10·9%). This salt also gave the picrate, m. p. and mixed m. p. 220—221°. The hydrogen sulphate, when warmed with sodium dichromate in 10% sulphuric acid, readily gave the trioxo-derivative (IX), m. p. and mixed m. p. 185—187° (from ethanol).

(iii) A solution of the hydrochloride in glacial acetic acid, when similarly boiled and then evaporated, gave colourless crystals, presumably the acetate (XV; X = $C_2H_3O_2$), which in turn afforded the picrate, m. p. and mixed m. p. 219—220°, and the hydrogen sulphate, m. p. and mixed m. p. 225—227°.

The hydrochloride (XIV; X = Cl), when heated at 180—190°/0·0001 mm., gave a yellow sublimate, m. p. *ca.* 205° (probably aniline hydrochloride). The residue, dissolved in ethanol, gave the picrate, m. p. and mixed m. p. 220—221°. The hydrochloride (XIV; X = Cl) charred extensively when heated with zinc chloride.

Synthesis of the Picrate (XV; X = $C_6H_2O_7N_3$).—Pure *iso*quinoline was converted by bromine in hydrobromic acid [17] into 4-bromo*iso*quinoline, b. p. 149°/13 mm., which with ammonia and copper sulphate [18] gave 4-amino*iso*quinoline, m. p. 106—108° (lit.,[18] 108·5°) from benzene. A solution of the 4-amino-compound in methanolic methyl iodide, when boiled under reflux for 5 min. and cooled, deposited 4-amino-2-methyl*iso*quinolinium iodide (XV; X = I) as a yellow powder, which was converted into the picrate (XV; X = $C_6H_2O_7N_3$), yellow needles, m. p. 219—221° (from ethanol). This sample was used for mixed m. p. purposes. A methanolic solution of the iodide when treated with perchloric acid deposited the *perchlorate* (XV: X = ClO_4), pale yellow, m. p. 183—184° (E.T.) (from ethanol) (Found: C, 46·6; H, 4·8; N, 10·9. $C_{10}H_{11}O_4N_2Cl$ requires C, 46·4; H, 4·3; N, 10·8%).

A mixture of the keto-amine hydrochloride (3·2 g.) and *N*-methyl-*N*-phenylhydrazine (2·0 g.) in ethanol (20 c.c.) was shaken under nitrogen for 6 hr. A trace of yellow silky crystals was collected, and the dark green filtrate diluted with ether, precipitating a yellow powder, m. p. 285° (decomp.) (T.I. 240°) (from ethanol–ether). This powder, treated with ethanolic sodium picrate, gave the picrate (XV; X = $C_6H_2O_7N_3$), m. p. and mixed m. p. 219—222° (T.I. 210°) (Found: C, 50·0; H, 3·9; N, 17·9%), and with perchloric acid gave the perchlorate (XV; X = ClO_4), m. p. and mixed m. p. 184° (E.T.) (Found: C, 46·3; H, 4·2; N, 10·7%).

A similar experiment using *N*-ethyl-*N*-phenylhydrazine gave indefinite results, but the yellow oil left after removal of unchanged reagents at 200°/0·001 mm. gave with ethanolic picric acid the picrate (XV; X = $C_6H_2O_7N_3$), m. p. and mixed m. p. 219° (Found: C, 49·9; H, 3·3; N, 18·0%).

A suspension of the keto-amine hydrochloride (1 g.) and powdered 2 : 4-dinitrophenylhydrazine (1 g.) in ethanol (20 c.c.) was shaken under nitrogen for 8 hr., an orange solid slowly separating. The reaction was incomplete after 5 days, so the mixture was warmed for 10 min., then cooled, and the orange crystalline insoluble *dinitrophenylhydrazone* (1 g.), m. p. 213° (decomp.) (T.I. 205°), was collected (Found: C, 54·6; H, 4·6; N, 20·5. $C_{16}H_{15}O_4N_5$ requires C, 56·3; H, 4·4; N, 20·5%. Low and inconsistent carbon values were obtained). A suspension in ethanolic hydrogen chloride was boiled for 90 min., then cooled, and the chloride (XV; X = Cl) was precipitated by ether. It was converted into the picrate (XV; X = $C_6H_2O_7N_3$), m. p. and mixed m. p. 219—222°.

A solution of the keto-amine (0·2 g.) in ethanol (1 c.c.) was added to a solution of semicarbazide hydrochloride (0·2 g.) and anhydrous sodium acetate (0·2 g.) in water (1 c.c.), which was boiled for 15 min. Cooling deposited the colourless *semicarbazone*, m. p. 207—209° (from ethanol) (Found: C, 60·4; H, 6·9; N, 25·7. $C_{11}H_{14}ON_4$ requires C, 60·5; H, 6·5; N, 25·7%). A solution of this in ethanolic hydrogen chloride was boiled under reflux for 40 min., and then afforded as before the picrate (XV; X = $C_6H_2O_7N_3$), m. p. and mixed m. p. 218—221° (T.I. 215°).

---

[17] Bergstrom and Rodda, *J. Amer. Chem. Soc.*, 1940, **62**, 3030.
[18] Craig and Cass, *ibid.*, 1942, **64**, 783.

3-*Benzylidene*-1 : 2 : 3 : 4-*tetrahydro*-2-*methyl*-4-*oxo*iso*quinoline* (*as* XVII).—A mixture of the base (II) (0·5 g.), benzaldehyde (0·3 g., 1 mol.), 10% aqueous sodium hydroxide (1·3 c.c.), and ethanol (0·6 c.c.) was thoroughly shaken under nitrogen and set aside for 16 hr., a red oil slowly separating and forming a yellow solid. The mixture was dissolved in a minimum of ethanol, and the *benzylidene derivative* reprecipitated by the addition of water: recrystallisation from aqueous ethanol (*ca.* 1 : 1) gave pale yellow needles (0·5 g., 60%) (Found: C, 81·6; H, 6·3; N, 5·9. $C_{17}H_{15}ON$ requires C, 81·9; H, 6·1; N, 5·6%). The compound slowly decomposed on exposure to air, with liberation of benzaldehyde. It gave a *picrate*, pale yellow plates, m. p. 197° from ethanol (Found: C, 57·7; H, 4·0; N, 12·1. $C_{17}H_{15}ON,C_6H_3O_7N_3$ requires C, 57·7; H, 3·8; N, 11·7%). The white hydrochloride, m. p. 210°, was precipitated when hydrogen chloride was passed into an ethereal solution of the benzylidene derivative.

The 3-p-*dimethylaminobenzylidene derivative* (XVII A–B) was similarly prepared, the mixture being set aside under nitrogen for 5 days. The orange-red crystalline deposit was then increased by cautious addition of water, and when collected and crystallised from aqueous ethanol (9 : 1 by vol.) gave orange crystals, m. p. 125—132° (Found: C, 77·7; H, 6·7; N, 9·8. $C_{19}H_{20}ON_2$ requires C, 78·0; H, 6·9; N, 9·6%). The cautious addition of aqueous-ethanolic perchloric acid to an ethanolic solution until the latter became colourless, followed by the addition of ether, precipitated the *diperchlorate*, colourless needles from ethanol (Found: C, 46·3; H, 4·9; N, 5·9. $C_{19}H_{20}ON_2,2HClO_4$ requires C, 46·3; H, 4·5; N, 5·7%). The colourless hydrochloride, similarly prepared, was too highly deliquescent for ready purification.

The 3-*p*-dimethylaminophenylimino-derivative was similarly prepared by using *p*-nitrosodimethylaniline, with ice-cooling during the mixing: after 1 day, the red crystals were collected but rapidly decomposed.

Reactions of the 3-*Ethoxycarbonyl Compound* (VIII).—*Oxidation.* This was carried out with sulphuric acid–sodium dichromate, as that of the keto-amine (II), and afforded *N*-methylphthalimide (X), identified as before.

Dehydrogenation. The base (VIII) was added dropwise to a vigorously shaken, cold, saturated aqueous solution of cupric acetate. A white powder was precipitated, and the blue colour, which had faded, was just restored by addition of more acetate solution. The filtered solution was divided into three portions. (i) Cautious addition of 60% perchloric acid diluted with a small quantity of ethanol precipitated the colourless *perchlorate* (XVIII; $X = ClO_4$), m. p. 157—158° after crystallisation from ethanol (Found: C, 47·0; H, 4·4; N, 4·1. $C_{13}H_{14}O_7NCl$ requires C, 47·1; H, 4·3; N, 4·2%). (ii) The addition of ethanolic picric acid gave the *picrate* (XVIII; $X = C_6H_2O_7N_3$), m. p. 172° after repeated crystallisation from ethanol (Found: C, 49·6; H, 3·8; N, 12·4. $C_{19}H_{16}O_{10}N_4$ requires C, 49·6; H, 3·5; N, 12·2%). (iii) The solution, mixed with 18% hydrochloric acid, was boiled under reflux for 8 hr. and evaporated to dryness: the residue, treated with sodium picrate, both in aqueous solution, deposited the picrate (XII; $X = C_6H_2O_7N_3$), m. p. and mixed m. p. 227° (E.T.) (from ethanol) (Found: C, 50·1; H, 3·7; N, 14·1%).

Reaction with hydrazine and phenylhydrazine. For clarity, the names of these compounds are based on the structure (XIX); in the analytical results, the theoretical values are given for this structure and then for the structure (XX A–B).

A solution of the base (VIII) (1 g.) and 65% aqueous hydrazine (2 c.c., 8 mol.) in ethanol (10 c.c.) was heated under reflux for 30 min., and the red solution cooled and diluted with ether, which precipitated the red 1 : 2 : 3 : 4-*tetrahydro*-2-*methyl*-5′-*oxopyrazolino*(4′ : 3′-3 : 4)iso*quinoline* (XIX; R = H), m. p. 290° (slight preliminary decomp.) after three such reprecipitations (Found: C, 65·3; H, 5·0; N, 21·2. $C_{11}H_{11}ON_3$ requires C, 65·7; H, 5·5; N, 20·9. $C_{11}H_9ON_3$ requires C, 66·3; H, 4·5; N, 21·1%). An ethanolic solution when treated with dry hydrogen chloride deposited the pale yellow hydrochloride, m. p. 266° (becoming red) (from ethanol).

A similar experiment, with phenylhydrazine (10 mol.) and heating for 4 hr., gave by ethereal precipitation the deep red 1′-*phenyl derivative* (XIX; R = Ph), m. p. 234° (from ethanol) (Found: C, 73·95; H, 5·3; N, 15·2. $C_{17}H_{15}ON_3$ requires C, 73·6; H, 5·5; N, 15·2. $C_{17}H_{13}ON_3$ requires C, 74·2; H, 4·8; N, 15·3%). The *hydrochloride*, prepared as above, formed fine yellow needles, m. p. 231° (E.T.) after crystallisation from ethanol containing hydrogen chloride (Found: C, 64·9; H, 4·7; N, 13·4. $C_{17}H_{15}ON_3,HCl$ requires C, 65·1; H, 5·1; N, 13·4. $C_{17}H_{13}ON_3,HCl$ requires C, 65·5; H, 4·5; N, 13·5%). The yellow *picrate*, twice recrystallised from a very dilute picric acid solution in ethanol, had m. p. 229° (Found: C, 55·4; H, 3·5; N, 17·1. $C_{17}H_{15}ON_3,C_6H_3O_7N_3$ requires C, 54·5; H, 3·6; N, 16·6. $C_{17}H_{13}ON_3,C_6H_3O_7N_3$ requires C, 54·8; H, 3·2; N, 16·7%). A solution of the pyrazolone in methyl iodide was boiled under reflux for 4 hr. and allowed to evaporate. The yellow crystalline residue afforded the *methiodide*, having m. p. 245° (decomp. from 233°) after two crystallisations from methanol (Found: C, 50·9; H, 4·0; N, 9·7. $C_{18}H_{18}ON_3I$ requires C, 51·6; H, 4·3; N, 10·0. $C_{18}H_{16}ON_3I$ requires C, 51·8; H, 3·9; N, 10·1%).

The use of a smaller proportion of hydrazine and of phenylhydrazine (*e.g.*, 2—3 mols.) in the above experiments gave crude products from which crystalline derivatives could not be isolated.

1 : 3-*Diphenylpyrazol*-5-*one*.—The product obtained by interaction of phenylhydrazine and ethyl benzoylacetate (1 mol.) on gentle warming was poured into ether, and the precipitated solid pyrazolone was triturated with ether, collected, and recrystallised from ethanol; it had m. p. 135—138° (lit.,[19] 137°) (Found: C, 76·2; H, 5·0; N, 12·1. Calc. for $C_{15}H_{12}ON_2$: C, 76·2; H, 5·1; N, 11·9%).

Ethyl o-*Chloromethylbenzoate and Aniline*.—The benzoate (7 g.) and aniline (7 g., 2 mol.), when mixed at room temperature, gave a crystalline deposit within 30 min. After 5 hr. the deposit was extracted with ether, leaving aniline hydrochloride (1·45 g.), m. p. 190°. Evaporation of the ethereal extract afforded a residue which when washed with ether (5 c.c.) gave the crystalline 1-oxo-2-phenyl*iso*indoline (XXII), m. p. and mixed m. p. 158—161°.

o-*Chloromethylbenzonitrile and Aniline*.—(*A*) A mixture of the nitrile, m. p. 54·5° (6 g.), and aniline (14 g., 4 mol.) was heated on a steam-bath for 1 hr., and the black product cooled in ice and neutralised with 10% aqueous sodium hydroxide, giving a black oil under the clear aqueous solution which was then decanted. The oil, when repeatedly shaken with water (2—3 l.), formed a brown solid, which after several recrystallisations from ethanol (charcoal) gave 2-phenyl-2-phenylimino*iso*indoline (XXIII), needles, m. p. 123—130° from room temperature, 150—153° (E.T.) (Found: C, 84·6; H, 6·0; N, 10·0. Calc. for $C_{20}H_{16}N_2$: C, 84·5; H, 5·7; N, 9·9%). An ethereal solution, treated with hydrogen chloride, gave the hydrochloride, m. p. 237—239° (lit.,[20] 237—238°).

(*B*) A solution of the nitrile (45 g.) and aniline (45 c.c., 1·5 mol.) in ethanol (185 c.c.) was heated under reflux for 1 hr., cooled, and poured into ether (1800 c.c.), precipitating the crude hydrochloride (62 g.) of the nitrile (XXV). A solution of this salt in water (500 c.c.), treated with 10% aqueous sodium hydroxide (1 mol.), deposited *N*-2-cyanobenzylaniline (XXV), (48 g., 75%), m. p. 114—121°.

Ethyl Ester of N-2-*Cyanobenzyl*-N-*phenylglycine* (XXVI).—A mixture of the crude nitrile (XXV) (60 g.) and ethyl bromoacetate (70 g., 1·3 mol.) was heated on a steam-bath for 30 min., ethanol (30 c.c.) being added after the first 10 min. The cold solution was poured into ether (2 l.), and the solution decanted from the precipitated black gum. A solution of the gum in water (2·5 l.), after being vigorously shaken (charcoal), gave a pink filtrate, which when treated with 10% aqueous sodium hydroxide (120 c.c.) deposited an oil which solidified. Repeated recrystallisation from 50% aqueous ethanol gave the *ethyl ester* (XXVI) (2·5 g.), m. p. 114·5—115·5° (Found: C, 73·3; H, 6·0; N, 9·6. $C_{18}H_{18}O_2N_2$ requires C, 73·5; H, 6·2; N, 9·5%). It gave a *perchlorate*, m. p. 132—134° (from ethanol) (Found: C, 54·6; H, 4·7; N, 7·2. $C_{18}H_{18}O_2N_2,HClO_4$ requires C, 54·8; H, 4·8; N, 7·1%), and a *picrate*, yellow needles, m. p. 167—170° (from ethanol) (Found: C, 55·1; H, 4·4; N, 13·5. $C_{18}H_{18}O_2N_2,C_6H_3O_7N_3$ requires C, 55·1; H, 4·0; N, 13·4%).

The mother-liquors from the recrystallisation of the ester (XXVI) were concentrated and cooled, giving a second crystalline crop (15 g.) which was recrystallised from 50% aqueous ethanol until the m. p. 101—110° (E.T.) was unchanged. The powdered material was extracted with cold dilute sulphuric acid, and the insoluble residue, when recrystallised as before, gave the *iso*indoline (XXII), m. p. and mixed m. p. 160—165° (E.T.).

Attempted Cyclisation.—The pure ester (XXVI) (0·5 g.) was added to a cold solution of sodium ethoxide prepared from sodium (0·5 g.) and ethanol (10 c.c.), which was then heated under reflux in nitrogen for 4 hr., cooled, poured into water (150 c.c.), and set aside overnight. The precipitated solid when collected and recrystallised from ethanol gave the *iso*indoline (XXII) (0·13 g.), plates, m. p. and mixed m. p. 160—166° (E.T.).

Dropwise addition of bromine water to an ethanolic solution of the ester (XXVI), followed

---

[19] Knorr and Klotz, *Ber.*, 1887, **20**, 2546.

[20] Thiele and Schneider, *Annalen*, 1909, **369**, 297.

by considerable dilution with dilute aqueous sodium carbonate, gave a crystalline *monobromo-derivative*, m. p. 157—159° (E.T.), shrinking at 145° (Found: C, 57·4; H, 4·7; N, 7·6. $C_{18}H_{17}O_2N_2Br$ requires C, 57·9; H, 4·6; N, 7·5%).

We gratefully acknowledge valuable discussions with Dr. N. Sheppard, and a grant (to I. G. H.) provided by the Department of Scientific and Industrial Research.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August 29th,* 1958.]