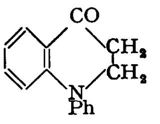
420. *The Structure and Properties of Certain Polycyclic Indolo- and Quinolino-derivatives. Part II.* Derivatives of 1-Ketojulolidine.*†

By Frederick G. Mann and Bryan B. Smith.

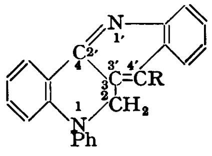
The synthesis of 1-ketojulolidine and of 1 : 6-diketojulolidine is described. The former condenses with isatin in alkaline solutions to give quinolino(2′ : 3′-1 : 2)juloline-4′-carboxylic acid which on decarboxylation furnishes quinolino-(2′ : 3′-1 : 2)juloline. This base exists in two isomeric forms : the yellow form can be converted *via* its salts into the orange form, and the latter when heated reverts to the yellow form. Both are readily oxidised to 3-ketoquinolino-(2′ : 3′-1 : 2)juloline. The probable structure of these forms and their derivatives is discussed.

1-Ketojulolidine phenylhydrazone undergoes indolisation to form ψ-indolo-(2′ : 3′-1 : 2)juloline.

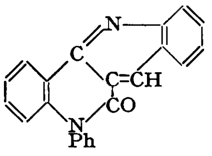
It has been shown by Mann (*J.*, 1949, 2816*) that 1 : 2 : 3 : 4-tetrahydro-4-keto-1-phenylquinoline (I), when subjected to the Pfitzinger reaction with isatin, gives 1 : 2-dihydro-1-phenylquinolino(3′ : 2′-3 : 4)quinoline-4′-carboxylic acid (II; R = CO_2H) which forms deep-red crystals, but gives yellow salts with alkalis. The acid on decarboxylation gives 1 : 2-dihydro-1-phenylquinolino(3′ : 2′-3 : 4)quinoline (II; R = H) as deep-yellow crystals which give deep red salts with acids. The base (II; R = H) undergoes a very ready atmospheric oxidation to 1 : 2-dihydro-2-keto-1-phenylquinolino(3′ : 2′-3 : 4)quinoline (III).



(I.)



(II.)



(III.)

It is noteworthy moreover that the phenylhydrazone of the ketone (I), when subjected to the Fischer indolisation, gives 1-phenyl-ψ-indolo(3′ : 2′-3 : 4)quinoline (IV), a reaction which is precisely similar to that which the phenylhydrazone of the parent 1 : 2 : 3 : 4-tetrahydro-4-keto-quinoline itself undergoes (Clemo and Perkin, *J.*, 1924, **125**, 1608). The structure of the compound (IV) has subsequently been independently confirmed by Dr. R. N. Haszeldine, who finds that its infra-red absorption spectrum shows no indication of an ‒NH‒ band in the 3-μ. region, whereas this band is present in the spectrum of its hydrochloride.

This and the following two papers report the preparation of other cyclic ketones similar in type to (I) and their conversion into the corresponding quinolino-derivatives, both for a study of the colour changes involved in this process and also (more particularly) for an investigation of the structural factors that determine the ready oxidation of these derivatives. The Fischer indolisation of the phenylhydrazones of these cyclic ketones has also been investigated.

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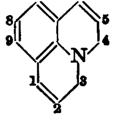
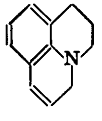
* *J.*, 1949, 2816, is regarded as Part I of this series.

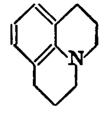
† Following the Editor's advice, the following names are adopted for the three amines having this ring system :



(A) Juline



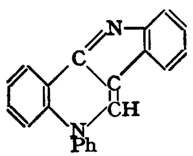
(B) Juloline

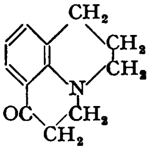


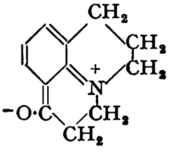
(C) Julolidine

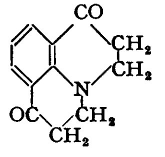
For earlier work concerning the preparation, naming, and numbering of these systems, see Reissert (*Ber.*, 1891, **24**, 844), Kayser and Reissert (*Ber.*, 1892, **25**, 1193), Pinkus (*ibid.*, p. 2798), von Braun *et al.* (*Ber.*, 1918, **51**, 1215). Reissert used the terms julole, juloline, and julolidine for these amines : the term juline has now been employed in place of julole, since the suffix of the latter term implies a five-membered ring.

It has been claimed (F. P. 806,715) that 1-2′-cyanoethyl-1 : 2 : 3 : 4-tetrahydroquinoline, when heated with a mixture of aluminium chloride, potassium chloride, and sodium chloride, ultimately yields 1-ketojulolidine (V). A similar claim, for use of aluminium chloride with chlorobenzene as a solvent, has been made in FIAT Final Report No. 1298 (1949). We have been unable to obtain the ketone (V) by this method : however, hydrolysis of the cyanoethyl derivative gave 1-2′-carboxyethyl-1 : 2 : 3 : 4-tetrahydroquinoline, which could readily be cyclised in xylene solution by phosphoric anhydride to the ketone (V).


(IV.)


(V.)

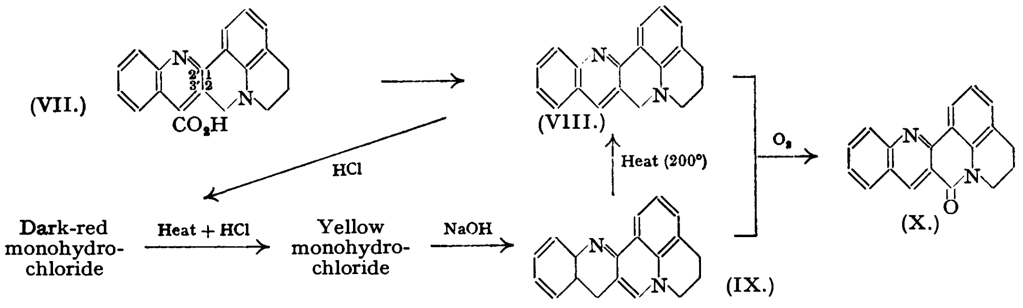

(V*A*.)


(VI.)

In marked contrast to this behaviour, however, we have found that *NN*-bis-2-cyanoethylaniline, $\mathrm{Ph{\cdot}N(CH_2{\cdot}CH_2{\cdot}CN)_2}$ (Cookson and Mann, *J.*, 1949, 67), when heated in chlorobenzene solution with aluminium chloride, gave 1 : 6-diketojulolidine (VI) in good yield, whereas the phosphoric anhydride cyclisation of the corresponding aniline-*NN*-bispropionic acid afforded this diketone in only very small yield.

It is noteworthy that, whereas julolidine readily forms both salts with acids and quaternary salts (Pinkus, *loc. cit.*), the nitrogen atom in the keto-amine (V) is almost neutral : for example, salts even with strong acids are difficult to isolate (the hydrochloride readily dissociates) and quaternary salts are not formed under the usual conditions. Both this low reactivity and the yellow colour of the ketone are presumably due to the contribution of the polar quinonoid form (V*A*).

1-Ketojulolidine (V) bears an obvious structural resemblance to the ketone (I), and its behaviour in the Pfitzinger reaction has therefore been studied. When solutions of the ketone (V) and of isatin in ethanolic potassium hydroxide are boiled under nitrogen, acidification ultimately yields quinolino(2′ : 3′-1 : 2)juloline-4′-carboxylic acid (VII), which when initially prepared was maroon in colour and gave red solutions in methanol and ethanol, but gave yellow solutions on treatment with alkali. It is probable that the explanation of the difference in colour of this acid and its salts is precisely parallel to that already given for the acid (II) (Mann, *loc. cit.*). The acid (VII) undergoes rapid oxidation on exposure to air and ultimately becomes yellowish-brown. The freshly precipitated acid was therefore decarboxylated by heat in a vacuum, and quinolino(2′ : 3′-1 : 2)juloline (VIII) obtained after sublimation and recrystallisation as bright yellow plates, m. p. 150°. The assignment of the structure (VIII) to this yellow base is discussed below.



The behaviour of the yellow base on salt formation is noteworthy. When dilute hydrochloric acid is added to an acetone solution of the base, deep red crystals of the hydrated monohydrochloride of the base separate : when, however, hydrogen chloride is passed into an ethanolic solution of the base, a deep red colour rapidly forms but later fades, and the solution becomes colourless as saturation with hydrogen chloride is attained. Colourless crystals, presumably of the dihydrochloride of the base, now separate : they dissociate to the red salt so rapidly on removal from the saturated acid solution that analysis was not practicable. The addition of limited quantities of toluene-*p*-sulphonic acid to a solution of the yellow base also produces a deep red colour. This behaviour with acids is in marked contrast with that shown on quaternisation. When the base is boiled with a large excess of methyl iodide, a cream-coloured crystalline monomethiodide is obtained. Treatment of the base with methyl toluene-*p*-sulphonate similarly gives a very pale lemon-yellow crystalline monomethotoluene-*p*-sulphonate, which can be readily converted into monomethiodide and hence has the same general structure. This marked difference between the deep red monohydrochloride and the almost colourless monoquaternary salts indicates an almost certain difference in structure.

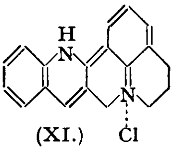
When, however, the deep-red solution of the monohydrochloride of the yellow base is boiled, the solution rapidly becomes yellow. If this solution is now basified, a crystalline orange base (*e.g.*, IX), m. p. 190°, isomeric with the yellow base (VIII), is isolated. Cooling the solution before basification gives the yellow crystalline monohydrochloride of the orange base : this salt has m. p. 388°, and its identity has been confirmed by its preparation direct from the pure orange base. This orange base also gives a yellow crystalline monotoluene-*p*-sulphonate, and also on quaternisation a monomethiodide and a monomethotoluene-*p*-sulphonate, both of which form bright yellow crystals. It is clear therefore that the salts formed from the isomeric yellow and orange bases are quite distinct.

Finally when the orange base was heated at 200° in a vacuum, it was readily converted back into the yellow base.

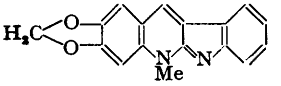
One further important relationship exists between the yellow and the orange base. The yellow base, when heated at 110° in a stream of air, underwent oxidation to 3-ketoquinolino-(2′ : 3′-1 : 2)juloline (X) ; the same oxidation occurred when the base was treated with an acetone solution of potassium permanganate, and also when a benzene solution of the base was exposed to the air for *ca.* one week. This oxidation is clearly parallel to that of the quinolino-derivative (II ; R = H) to the ketone (III), and it is by analogy with the unambiguous structure of (III) that the oxidation in the compound (X) is considered to have occurred in the (corresponding) 3-position. The oxidation of the orange base gives the same product but much more readily : for instance, a sample of the orange base underwent complete oxidation when exposed in benzene solution to the air at room temperature for 3 hours. It is noteworthy that although the keto-base (X) would form salts with hydrochloric and toluene-*p*-sulphonic acids, it would not form quaternary salts. Furthermore the quaternary methotoluene-*p*-sulphonates of the yellow and the orange base would not undergo oxidation similar to that of the parent bases themselves. These results are to be expected in view of the structure of the keto-base (X), where the julolidine nitrogen atom is now part of a cyclic acid amide and thus could not form salts : hence furthermore the strong protection afforded to the 3-methylene group of the two bases by quaternisation at this nitrogen atom. The salt formation which the keto-base undergoes with acids undoubtedly occurs at the quinolino-1′-nitrogen atom. This again is parallel to the behaviour of the quinolino-derivative (II ; R = H) which readily forms salts with acids at the 1′-nitrogen atom but does not form quaternary salts under the usual conditions.

We have at present no decisive explanation for the behaviour of the yellow base with acids and with alkyl halides, or for the isomerism of the yellow and the orange base. The following points must be considered, however. The fact that the yellow base forms deep red salts with one equivalent of acids but very pale yellow quaternary salts indicates strongly that a marked change in structure occurs on salt formation with acids but not apparently on quaternary salt formation. Since julolidine itself readily forms quaternary salts whereas the quinolino-1′-nitrogen atom in the base (II ; R = H) and in the keto-bases (III) and (X) does not, it is reasonably certain that quaternisation of the yellow base occurs normally at the julolidine nitrogen atom, and hence is accompanied by no fundamental change in structure.

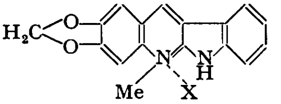
It is probable moreover that the red salt formed from one equivalent of an acid and the yellow base is due to the latter acting as an "anhydronium base," and that the mono-hydrochloride has the structure (XI), which would almost certainly cause intense colour. A number of such anhydronium bases have been described by Armit and Robinson (*J.*, 1925, **127**,



(XI.)



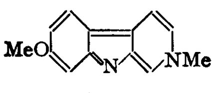
(XII*A*.)



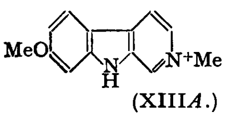
(XII*B*.)

1604) : for example, one somewhat similar to our yellow base is the compound (XII*A*) which will add on even water to give the quaternary hydroxide (XII*B* ; X = OH), and will give salts with acids in the same way. Similarly methylnorharmine (XIII) on treatment with acids gives the cation (XIII*A*) (Perkin and Robinson, *J.*, 1919, **115**, 951).

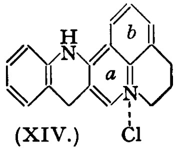
It should be noted, however, that salt formation by the anhydronium bases cited by Robinson causes a shift in valencies which gives the molecule a more highly aromatic character and hence a greater stability. We suggest that in our heterocyclic system the formation of the unstable red monohydrochloride (XI) is an intermediate stage in this process, and that the ready isomerisation which occurs when this red salt is boiled in aqueous solution is caused by its conversion into a salt of structure (XIV). This conversion, by making both the rings *a* and *b* aromatic in type, would enhance the stability of the salt : the simultaneous loss of the quinonoid structure would of course account for the decrease in intensity of the colour of the salt (from red to yellow). Basification of the stable yellow salt (XIV) would then produce the orange base (IX).



(XIII.)

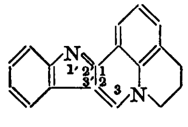


(XIII*A*.)

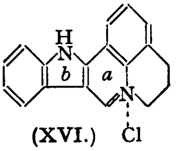


(XIV.)

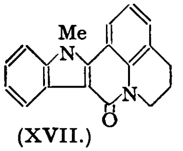
The indolisation of the phenylhydrazone of 1-ketojulolidine has been investigated under the action of dilute sulphuric acid (cf. Clemo and Perkin, *loc. cit.*) and of aqueous-ethanolic hydrogen chloride (cf. Mann, *loc. cit.*). The former reagent gives a crystalline product, m. p. 198—199°, for which satisfactorily consistent analyses have not been obtained, but which is almost certainly the ψ-indole (XV), the reaction apparently proceeding precisely similarly to the conversion of the phenylhydrazone of the ketone (I) into the ψ-indole (IV). The evidence for the ψ-indole structure (XV) rests on the following points. (i) The compound forms bright yellow crystals, whereas the indole (had indolisation proceeded normally) would probably be colourless. (ii) These yellow crystals, however, readily give a colourless hydrochloride and methiodide, for which analyses indicate the addition of these units to the ψ-indole (XV). It would be expected that, for example, hydrogen chloride would readily add to the ψ-indole (XV) to give a salt structure (XVI)—and that methyl iodide would add similarly—since by this addition the rings *a* and *b* acquire aromatic character; furthermore the structure of these salts would almost certainly cause them to be colourless. On the other hand, if the yellow crystals were a true indole, salt formation could only occur by normal proton addition at the julolidine nitrogen atom, a process which should cause no change in colour. (iii) The examination of the infra-red spectrum of the yellow crystals in the 3-μ. region gives no indication of the –NH– band which the true indole should show, but the colourless monohydrochloride shows this band at 2·94 μ. in accordance with the structure (XVI).



(XV.)



(XVI.)



(XVII.)

When the indolisation of the phenylhydrazone was carried out with aqueous-ethanolic hydrogen chloride, the above yellow compound, m. p. 198—199°, was again the main product, but by careful fractional crystallisation a very small yield of another compound, m. p. 224°, identical in appearance with the former compound was isolated. Analysis indicated that this compound was probably isomeric with the former, and its infra-red spectrum also indicated that it did not contain the –NH– band. It is therefore apparently also a ψ-indole. No thermal interconversion of these compounds was observed, nor was any evidence of oxidation of either to a keto-derivative, similar in type to (X), detected : this oxidation would not of course be expected in a ψ-indole of structure (XV). The very small amount of the compound of m. p. 224° available precluded a more detailed investigation of its structure, which at present remains uncertain.

When the methylphenylhydrazone of 1-ketojulolidine was subjected to indolisation with dilute sulphuric acid, the m. p. of the crude base isolated indicated that it was a mixture :

extensive recrystallisation ultimately furnished, however, the pure colourless 3-keto-1′-methylindolo(2′ : 3′-1 : 2)juloline (XVII). The structure of this compound is supported by its infrared spectrum, which shows carbonyl absorption at 6·12 μ. which is consistent with the structure (XVII), whereas there is no indication in the 3-μ. region of absorption due to OH groups which might conceivably have been formed by oxidation. It is clear that in this case the true indole—like the quinolino-derivatives (VIII) and (IX)—is very readily oxidised, and that the crude product was almost undoubtedly a mixture of the initial unoxidised indole and the oxidised keto-derivative (XVII), from which the latter alone was isolated in the pure state. This ready oxidation, and the colourless nature of these methylindoles, differentiate them sharply from the stable yellow ψ-indole (XV).

EXPERIMENTAL.

Many of the compounds prepared in this investigation showed consistent m. p.s only when the substance was heated in a capillary tube which had been evacuated and sealed. Such determinations are indicated by an asterisk.

1-2′-*Cyanoethyl*-1 : 2 : 3 : 4-*tetrahydroquinoline*.—Tetrahydroquinoline, prepared by hydrogenation of pure synthetic quinoline over copper chromite (Adkins and Connor, *J. Amer. Chem. Soc.*, 1931, **53**, 1091), was boiled with vinyl cyanide in acetic acid under reflux (cf. B.P. 466,316/1937; Whitmore *et al.*, *J. Amer. Chem. Soc.*, 1944, **66**, 730). The cyano-derivative had b. p. 197—199°/14 mm.; the yield was 73%.

1-2′-*Carboxyethyl*-1 : 2 : 3 : 4-*tetrahydroquinoline*.—The cyano-derivative (247 g.) was added to a solution of potassium hydroxide (350 g.) in water (2·5 l.) and boiled under reflux until a clear solution was obtained (*ca.* 2·5 hours). The solution was cooled, and concentrated hydrochloric acid added until precipitation of the above *acid*, which separated initially as an oil which subsequently crystallised, was complete. (The presence of a slight excess of hydrochloric acid promotes this crystallisation, but a larger excess will of course redissolve the product.) The acid was collected, thoroughly washed with water, and dried, the yield being 240 g. (88%). This acid was sufficiently pure for the next stage: a sample when recrystallised from *cyclo*hexane formed colourless crystals, m. p. 69—71° (Found: C, 70·0; H, 7·5; N, 7·15. $C_{12}H_{15}O_2N$ requires C, 70·2; H, 7·4; N, 6·8%). The acid gave a *hydrochloride*, colourless crystals (from ethanol), m. p. 171·5° (Found: C, 59·5; H, 7·1; N, 5·5. $C_{12}H_{15}O_2N,HCl$ requires C, 59·6; H, 6·7; N, 5·8%).

1-*Ketojulolidine* (V).—Dry xylene (500 c.c.) and the above acid (71 g.) were added in turn to a mixture of phosphoric anhydride (50 g.) and " Hyflo Supercel " (porous silica powder) (25 g.), and the mixture was boiled under reflux with stirring for 1 hour. The xylene was decanted, and the residue extracted with boiling xylene (2 × 100 c.c.). The united xylene extracts were distilled, and the *ketone* obtained as a yellow distillate, b. p. 127—130°/0·2 mm., which readily crystallised in the receiver (20 g., 31%). Recrystallisation from *cyclo*hexane gave yellow needles, m. p. 62·5—63·5° (Found: C, 77·05; H, 7·1; N, 7·4. $C_{12}H_{13}ON$ requires C, 77·0; H, 7·0; N, 7·5%).

1 : 6-*Diketojulolidine* (VI).—A mixture of powdered aluminium chloride (30 g.), concentrated hydrochloric acid (1·5 c.c.), chlorobenzene (30 c.c.), and *NN*-bis-2-cyanoethylaniline (9 g.) was thoroughly stirred whilst heated at 140° for 6 hours. It was then cooled, hydrolysed with ice-water, and steam-distilled to remove the chlorobenzene. The cold heavy oily residue was extracted with chloroform, and the extract dried and distilled. The *diketone* was obtained as a yellow liquid, b. p. 190—210°/0·3 mm., which rapidly solidified (4·5 g.). Recrystallisation from ethanol gave bright yellow crystals, m. p. 145—146° (Found: C, 71·8; H, 5·4; N, 7·0. $C_{12}H_{11}O_2N$ requires C, 71·6; H, 5·5; N, 7·0%).

When a methanolic solution of the diketone (2 g.) containing a few drops of acetic acid was boiled with phenylhydrazine for a short time and cooled, yellow needles of the *osazone*, m. p. 248° (3·4 g.), separated. They were collected and washed with hot methanol, in which they were almost insoluble (Found: C, 75·15; H, 5·75; N, 18·7. $C_{24}H_{23}N_5$ requires C, 75·55; H, 6·05; N, 18·4%).

Quinolino(2′ : 3′-1 : 2)*juloline*-4′-*carboxylic Acid* (VII).—1-Ketojulolidine (14·9 g.) and isatin (13·4 g., 1·15 mols.) were added to a solution of potassium hydroxide (16 g., 3·5 mols.) in ethanol (87 c.c.) containing water (17·5 c.c.), and boiled under reflux in a nitrogen atmosphere for 15 hours. The cold filtered solution was added slowly with stirring to 10% acetic acid (200 c.c.) to precipitate the acid (VII); when crystallisation was complete, the acid was collected, washed with water and ethanol, and dried (yield, 13 g., 52%). The whole process of isolation of the acid was performed in a nitrogen atmosphere. The very ready atmospheric oxidation of this acid, and its very low solubility in most solvents, made purification very difficult. The highest m. p. recorded was 177·5—179°, but even this sample was still impure (Found: C, 74·8; H, 5·55; N, 8·7. Calc. for $C_{20}H_{16}O_2N_2$: C, 75·9; H, 5·1; N, 8·85%). It is noteworthy that, although a solution of the acid in methanol or ethanol was red, that in 2-methoxyethanol was yellow.

The potassium salt, isolated by adding the finely powdered base to 20% aqueous potassium hydroxide solution, separated as a yellow gum which could not be crystallised.

Quinolino(2′ : 3′-1 : 2)*juloline* (VIII).—(a) *The yellow base*. The acid (VII) (12 g.) was heated in a sublimation-still at 0·2 mm., with the bath-temp. at 250°. Decarboxylation followed by sublimation occurred; ultimately the sublimed base (9 g.) was obtained as a bright-yellow glass, which when once recrystallised from ethanol in a nitrogen atmosphere formed bright yellow plates (7·8 g.), sufficiently pure for further use. For analytical purposes, a sample was similarly recrystallised twice more, and then had m. p. 150° * [Found : C, 84·0; H, 5·9; N, 10·5%; *M* (ebullioscopic in benzene under nitrogen), 264. $C_{19}H_{16}N_2$ requires C, 83·8; H, 5·9; N, 10·3%; *M*, 272].

The yellow base gave the following derivatives :

Monohydrochloride. When dilute aqueous hydrochloric acid was added to a cold acetone solution of the base, the dihydrated *monohydrochloride* was precipitated as deep red crystals, which were collected, washed with acetone, and dried at room temperature in a vacuum (Found : C, 66·1; H, 6·2; N, 7·8. $C_{19}H_{16}N_2,HCl,2H_2O$ requires C, 66·2; H, 6·1; N, 8·1%). Attempts to dehydrate this compound by heat, or to recrystallise it, converted it into the hydrochloride of the orange base. On being heated in an evacuated capillary-tube, it underwent the following series of changes : *ca.* 200°, dark green, with drops of liquid (almost certainly water) condensing on the upper and cooler portions of the tube; *ca.* 250°, greenish-yellow; *ca.* 320°, dull yellow; *ca.* 350°, brown; ultimate m. p. 390°. It is almost certain that before melting it had been converted entirely into its isomeride.

When a current of hydrogen chloride was passed into an ethanolic solution of the yellow base, the solution rapidly became red but ultimately became colourless as saturation with the chloride was achieved, and colourless crystals separated. The latter were stable only in high concentrations of hydrogen chloride, and when separated from the solution rapidly dissociated. They were not therefore further investigated.

The red toluene-*p*-sulphonate of the yellow base so rapidly isomerised to that of the orange base (see below) that attempts to isolate it were abandoned.

Monomethiodide. A solution of the yellow base in an excess of methyl iodide was boiled under reflux for 5 hours and cooled. The *monomethiodide* which separated was collected, and twice recrystallised from ethanol in which it was sparingly soluble; it formed colourless needles, m. p. 173·5° * (decomp.) (Found : C, 57·7; H, 4·7; N, 7·0. $C_{20}H_{19}N_2I$ requires C, 58·0; H, 4·6; N, 6·8%).

*Monomethotoluene-*p*-sulphonate.* A mixture of the base with an excess of methyl toluene-*p*-sulphonate was heated in an evacuated sealed tube at 100° for 30 minutes. The excess of the ester was then extracted with ether, and the residual *sulphonate*, when thrice recrystallised from ethanol–ethyl acetate (1 : 6 by vol.), formed very pale lemon-yellow needles, m. p. 207° * (Found : C, 70·6; H, 5·5; N, 6·3. $C_{27}H_{26}O_3N_2S$ requires C, 70·7; H, 5·7; N, 6·1%). The addition of sodium iodide to an acetone solution of this salt precipitated the above monomethiodide, identified by m. p. (mixed and unmixed).

(b) *The orange base.* The yellow base was boiled with dilute hydrochloric acid; the solution, which was at first deep red, soon changed to a clear yellow with a green fluorescence. This solution was poured into an excess of warm dilute sodium hydroxide solution, and the precipitated orange *base* when cold was collected and recrystallised from ethanol under nitrogen. It was obtained as bright orange plates, m. p. 190° * [Found : C, 84·0; H, 5·7; N, 10·5%; *M* (ebullioscopic in benzene under nitrogen), 270]. A mixture of approximately equal amounts of the yellow and the orange base had m. p. 153—170° * The red dihydrated monohydrochloride of the yellow base showed the same behaviour when boiled with water or dilute hydrochloric acid.

The orange base gave the following derivatives :

Monohydrochloride. (*a*) The yellow base was boiled with dilute hydrochloric acid as above until the solution was yellow, cooling then caused the separation of the crystalline monohydrochloride of the orange base. This salt, when thrice recrystallised from ethanol, separated as yellow needles of the *hemiethanolate*, m. p. 388° (Found : C, 72·3; H, 6·3; N, 8·8. $C_{19}H_{16}N_2,HCl,0{\cdot}5C_2H_6O$ requires C, 72·4; H, 6·1; N, 8·45%). Heating at 100°/0·1 mm. for 6 hours gave the solvent-free *salt* of unchanged m. p. (Found : C, 73·7; H, 5·7; N, 9·25. $C_{19}H_{16}N_2,HCl$ requires C, 73·9; H, 5·55; N, 9·1%).

(*b*) The orange base was boiled with dilute hydrochloric acid, and the clear solution on cooling deposited the above monohydrochloride, which when similarly recrystallised had the same m. p. (alone and mixed). It should be emphasised that this hydrochloride can be obtained by the action of the cold acid on the orange base; the solubility of the hydrochloride is so low, however, that particles of the unchanged base tend to become covered with a protective layer of hydrochloride; warming was therefore employed to obtain a clear solution and hence complete conversion.

*Monotoluene-*p*-sulphonate.* (*a*) The yellow base and toluene-*p*-sulphonic acid (1 mol.) were mixed in ethanolic solution under nitrogen at room temperature, and set aside. The solution was deep red but deposited green crystals. The latter on recrystallisation from ethanol became first pale green and ultimately gave clear yellow crystals of the *monotoluene-*p*-sulphonate*, m. p. 253—260° (darkening and sintering at 237°), unchanged by further crystallisation (Found : C, 69·95; H, 5·4; N, 6·2. $C_{19}H_{16}N_2,C_7H_8O_3S$ requires C, 70·2; H, 5·4; N, 6·3%). The same salt was obtained by heating the yellow base with the acid (2 mols.) without a solvent in a sealed and evacuated tube.

(*b*) When the orange base was added to an ethanolic solution of toluene-*p*-sulphonic acid, a yellow solution with the green fluorescence characteristic of the salts of the orange base was at once obtained. The mixture was warmed to dissolve all the base and, on cooling, the sulphonate of the orange base crystallised; after purification it had the same indefinite m. p. (mixed and unmixed) as that prepared above.

Monomethiodide. When the orange base was boiled with an excess of methyl iodide, combination rapidly occurred; the precipitated *methiodide*, when twice recrystallised from methanol, formed yellow crystals, m. p. 220° * (decomp.) (Found : C, 57·9; H, 4·35; N, 7·0%).

*Monomethotoluene-*p*-sulphonate.* This was prepared precisely as that of the yellow base. Recrystallisation from ethyl methyl ketone gave bright yellow crystals of the *sulphonate*, m. p. 171—171·5° * (Found : C, 71·3; H, 5·6; N, 6·0%). This salt, treated with sodium iodide in acetone solution, was converted into the foregoing methiodide.

Conversion of the Orange Base into the Yellow Base.—The former was heated in a sealed evacuated tube at 200° for 20 minutes. The product, once recrystallised from ethanol, gave bright yellow plates of the yellow base, m. p. 149—149·5° (alone and mixed).

Oxidation of the Yellow Base.—(*a*) The finely powdered crystals were heated in a stream of air at 110° for 6 hours. The brown product was extracted with boiling methanol, and the extract then boiled with charcoal, filtered, and cooled. The 3-*ketoquinolino*(2′ : 3′-1 : 2)*juloline* (X) which separated was collected and after further recrystallisation from methanol gave cream-coloured needles, m. p. 177° (Found: C, 79·7; H, 5·0; N, 9·6. $C_{19}H_{14}ON_2$ requires C, 79·7; H, 4·9; N, 9·8%).

(*b*) A cold benzene solution of the base was exposed to the air at room temperature for one week, more benzene being added occasionally to replace that lost by evaporation. The solution was then allowed to evaporate to dryness, and the solid residue, when recrystallised from methanol, gave cream-coloured needles, m. p. 177°, alone and when mixed with the product from (*a*).

(*c*) A cold acetone solution of potassium permanganate was added dropwise to a similar solution of the yellow base (with intermittent centrifuging to separate the precipitated manganese dioxide) until a faint persistent colour remained. The decanted solution was evaporated, and the residue, once recrystallised from methanol, furnished the above oxidation product, m. p. 176·5—177° (alone and mixed).

Oxidation of the Orange Base.—The base, when exposed in benzene solution to the air at room temperature, underwent rapid oxidation. In one experiment, oxidation was complete in 3 hours, and the product after crystallisation from methanol was identical with that obtained from the yellow base and had the same m. p. (alone and mixed).

When toluene-*p*-sulphonic acid was added to an ethanolic solution of the ketone (X), the yellow crystalline *toluene*-p-*sulphonate* was precipitated, and after recrystallisation from ethanol had m. p. 203° (Found: C, 67·95; H, 4·9; N, 6·2. $C_{19}H_{14}ON_2,C_7H_8O_3S$ requires C, 68·1; H, 4·8; N, 6·1%).

The ketone (X) was unaffected when boiled with methyl iodide under reflux for 1 hour.

Attempted Hydrogenation of the Yellow Base.—A solution of the base, containing Adams's platinum catalyst, was subjected to hydrogen at 50 atms. for 6 hours at 80°, but the unchanged base, m. p. 144—147°, was subsequently recovered. The experiment was repeated at 100° using Raney nickel and hydrogen at 75 atms.: the solution became decolorised but on evaporation only an uncrystallisable pale yellow gum was obtained.

Attempted Oxidation of the Quaternary Salts.—For these experiments the monomethotoluene-*p*-sulphonates, and not the methiodides, had clearly to be employed. When the sulphonate of the yellow base was heated in a stream of air at 180° for 6 hours, a black tar resulted, and no well-defined product could be isolated. When a solution of the salt in aqueous acetone was treated with an acetone solution of potassium permanganate, some oxidation appeared to occur but no recognisable product could be isolated.

When the sulphonate of the orange base was heated in a stream of air at 125—150° for 4 hours, it was almost entirely unaffected. Attempted oxidation in acetone with permanganate again gave no definite product.

1-*Ketojulolidine Phenylhydrazone.*—A solution of the ketone (25 g.), phenylhydrazine (20 g., 1·4 mols.), and acetic acid (2 c.c.) in ethanol (125 c.c.) was boiled under reflux for 1·5 hours and then cooled. The *phenylhydrazone* (31 g., 84%) which separated formed pale yellow crystals from ethanol, m. p. 117·5° * (Found: N, 15·4. $C_{18}H_{19}N_3$ requires N, 15·15%).

Indolisation.—(a) *By aqueous sulphuric acid.* The phenylhydrazone (6 g.) was added to a warm mixture of concentrated sulphuric acid (12 c.c.) and water (108 c.c.), which was then boiled under reflux in a nitrogen atmosphere for 30 minutes and then set aside for 2 hours. The sulphate which had separated was collected, dissolved in hot water, and basified with 10% aqueous sodium hydroxide solution. The precipitated base was collected, thoroughly washed with boiling water, dried, and recrystallised five times from light petroleum (b. p. 60—80°)–ethanol (3·5 : 1 by vol.), all these operations being conducted under nitrogen. The pale yellow needles of the *ψ-indole* (XV), after drying at 85°/0·01 mm. for 1 hour, had m. p. 198—199°. The following analyses show the variation in carbon and hydrogen values for different samples all of which were prepared in this way and had almost identical m. p.s (Found: C, 83·1, 82·7, 82·1, 83·4; H, 5·7, 5·9, 6·0; N, 11·1. $C_{18}H_{14}N_2$ requires C, 83·7; H, 5·5; N, 10·8%).

Hydrochloride of the ψ-indole (XV). When ethanolic hydrogen chloride was added to an ethanolic solution of the yellow crystals, the *hydrochloride* was precipitated as colourless crystals, which when dried in a vacuum had m. p. 448° * (Found: C, 73·3; H, 5·4; N, 9·5. $C_{18}H_{14}N_2,HCl$ requires C, 73·3; H, 5·1; N, 9·5%).

The *methiodide* was readily formed when a solution of the yellow crystals in methanolic methyl iodide was boiled: the colourless crystals after recrystallisation from methanol and drying at 0·1 mm. had m. p. 364° * (Found: C, 56·9; H, 4·45. $C_{19}H_{17}N_2I$ requires C, 57·0; H, 4·3%).

(b) *By hydrogen chloride.* The hydrazone forms an almost insoluble hydrochloride in ethanolic hydrogen chloride. Consequently, a solution was prepared by boiling the hydrazone (5 g.) with saturated ethanolic hydrogen chloride (200 c.c.) previously diluted with water (125 c.c.). The colour of the solution rapidly became deep red and then faded to orange. After 4 hours' heating, the solution was filtered hot and set aside for 48 hours. A first crop of hydrochloride (1 g.) was then collected, and after 14 days a second crop which had slowly separated was also collected. The first crop was found to be richer in the high-melting base, whilst the second crop contained mainly the above low-melting base.

The first crop was basified by vigorous shaking with chloroform (5 c.c.) and 5% aqueous sodium hydroxide (5 c.c.), and the chloroform extract was dried and evaporated. The crude residual base was thrice recrystallised from ethanol; at each recrystallisation, the crystals were collected when about half the crop had separated. By these means the less soluble form of the *ψ-indole* was obtained pure as yellow crystals, which after being heated at 80°/0·2 mm. for 1·5 hours had m. p. 223—224°,* unchanged by further recrystallisation. The following show the variation in analytical results of different samples of the same m. p. (Found : C, 82·5, 83·3, 83·8, 82·6; H, 6·05, 5·9, 5·75, 5·9; N, 10·6%). When a saturated ethanolic solution of hydrogen chloride was added to a similar solution of this base, almost white crystals of the hydrochloride, m. p. 437° with preliminary darkening, separated; there was insufficient for analysis.

The second crop of hydrochloride from the indolisation was similarly converted into the base, which when recrystallised four times from ethanol gave yellow crystals; these after drying at 110°/0·2 mm. for 1 hour had m. p. 198·5—199·5°, unchanged either by two recrystallisations from benzene or by admixture with the base obtained in (a). Analytical results similar in range to those previously cited for this low-melting form were obtained on the compound prepared by this method.

The ψ-indole of m. p. 198° was recovered unchanged after the powdered crystals had been heated at 85° in an oxygen atmosphere for 1·5 hours, and also after a stream of oxygen was passed for 14 hours through a boiling solution of the base in light petroleum–ethanol. The precautions taken against atmospheric oxidation in the earlier experiments were therefore apparently unnecessary.

1-*Ketojulolidine Methylphenylhydrazone*.—This was prepared precisely as the phenylhydrazone, using, however, the ketone (7·8 g.), methylphenylhydrazine (7·4 g., 1·4 mols.), acetic acid (0·7 c.c.), and ethanol (40 c.c.). The crude *hydrazone* (9·3 g., 77% yield) after crystallisation from ethanol formed deep yellow crystals, m. p. 72° * (Found : C, 78·15; H, 7·7; N, 14·5. $C_{19}H_{21}N_3$ requires C, 78·3; H, 7·3; N, 14·4%).

Indolisation.—The hydrazone (5·4 g.) was boiled under reflux with a solution of sulphuric acid (10·8 c.c.) and water (100 c.c.) for 1 hour under nitrogen and then set aside over-night. The crystalline indole sulphate which separated proved initially difficult to decompose; the free base was ultimately isolated by slowly adding a solution of the sulphate in boiling water (100 c.c.) to a boiling aqueous 10% sodium hydroxide solution (200 c.c.). The mixture was then boiled vigorously for 10 minutes, then cooled, and the aqueous solution decanted from the pale yellow oil which had separated. This oil was boiled with water (100 c.c.) which was also decanted. The oil was dried by distillation of its suspension in light petroleum (b. p. 100—120°), during which process the non-volatile oil crystallised. These crude crystals, after two recrystallisations from ethanol, had m. p. 115—175°, then after one crystallisation from light petroleum (b. p. 100—120°), m. p. 175—205°, and finally after three more crystallisations from ethanol, m. p. 211—211·5°; the white crystals so obtained were the pure 3-*keto*-1′-*methylindolo*(2′ : 3′-1 : 2)*juloline* (XVII) (Found : C, 79·1; H, 5·5; N, 9·6. $C_{19}H_{16}ON_2$ requires C, 79·15; H, 5·6; N, 9·7%). A further recrystallisation from ethanol left the m. p. and composition unaltered (Found : C, 79·2; H, 5·45%). This compound in ethanolic solution readily gave a *picrate*, which after recrystallisation from ethanol furnished orange needles, m. p. 170—170·5° * (Found : C, 57·95; H, 3·5; N, 13·75. $C_{19}H_{16}ON_2,C_6H_3O_7N_3$ requires C, 58·0; H, 3·7; N, 13·5%). There is very little doubt, therefore, that in spite of the precautions taken to avoid atmospheric oxidation, the crude product consisted of the required methylindolo-compound and the oxidised product (XVII), and that the latter compound, being less soluble, was ultimately isolated in the pure state.

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