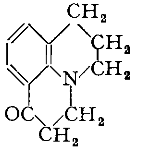
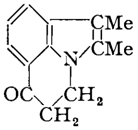
343. *The Structure and Properties of Certain Polycyclic Indolo- and Quinolino-derivatives. Part V.* Derivatives of* 1 : 2-*Dihydro*-1-*keto*-4 : 5-*dimethyl-liline.*†

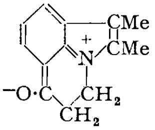
By C. Y. Almond and Frederick G. Mann.

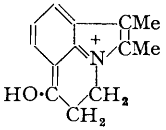
1-2′-Carboxyethyl-2 : 3-dimethylindole on cyclisation furnishes 1 : 2-dihydro-1-keto-4 : 5-dimethyl-liline. The properties of this compound have been investigated for comparison with those of other cyclic keto-amines, and particularly with those of the structurally analogous 1-ketojulolidine. The keto-liline gives a phenylhydrazone which furnishes a ψ-indole. The keto-liline, when subjected to the Pfitzinger reaction with isatin followed by decarboxylation, gives a quinolinoliline which, unlike the corresponding juloline derivative, does not show isomeric forms but resembles this derivative in undergoing ready oxidation to a cyclic amide.

Previous papers in this series (*J.*, 1949, 2816; 1951, 1898, 1906, 1909) have recorded investigations on the structure and properties of the indolo- and quinolino-derivatives obtained from various cyclic keto-amines and keto-sulphides by the Fischer indolisation and the Pfitzinger reactions respectively. In particular, it was shown by Mann and Smith (*J.*, 1951, 1898) that 1-ketojulolidine (I) (*a*) when converted into its phenylhydrazone and then indolised gives a ψ-indole, and (*b*) when subjected to the Pfitzinger reaction and then decarboxylated gives a quinolino-derivative which exists in two distinct and interconvertible isomeric forms, both of which, however, undergo very ready atmospheric oxidation to the same cyclic amido-derivative. Although the formation of a ψ-indole, and the ready oxidation of the quinolino-base, had been encountered with other similar polycyclic systems, the occurrence of isomerism in the quinolino-base and its derivatives was novel, and we have therefore investigated the properties of the corresponding derivatives obtained from 1 : 2-dihydro-1-keto-4 : 5-dimethyl-liline (II), in which the ring system differs from that of (I) only by the replacement of the hydrogenated pyridine ring by a pyrrole ring.


(I)


(II)


(II*a*)

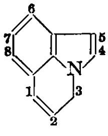

(III)

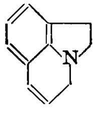
2 : 3-Dimethylindole, when heated with vinyl cyanide in the presence of sodium methoxide (B.P. 457,621), is readily converted into 1-2′-cyanoethyl-2 : 3-dimethylindole, but attempts to cyclise this nitrile directly to 1 : 2-dihydro-1-keto-4 : 5-dimethyl-liline by the action of aluminium chloride under various conditions [cf. F.P. 806,715; F.I.A.T. Final Report No. 1298 (1949); Mann and Smith, *loc. cit.*] gave unsatisfactory results. The

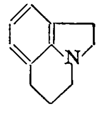
---

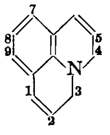
* Part IV, *J.*, 1951, 1909.

† *Note on Nomenclature.* Bamberger and Sternitzki (*Ber.*, 1893, **26**, 1298) gave the names liloline and lilolidine to the compounds (*B*) and (*C*) respectively. We have therefore termed the compound


(*A*) Liline

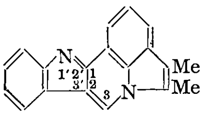

(*B*) Liloline


(*C*) Lilolidine

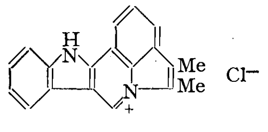

(*D*) Juline

(*A*) liline, and the names of the three compounds thus form a series corresponding to juline (*D*), juloline, and julolidine (cf. Mann and Smith, *J.*, 1951, 1898): the liline ring system is numbered as in (*A*) to correspond to that of juline (*D*).

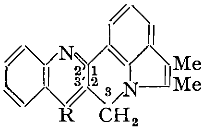
nitrile was therefore hydrolysed to 1-2′-carboxyethyl-2 : 3-dimethylindole, which with phosphoric anhydride in boiling xylene readily gave 1 : 2-dihydro-1-keto-4 : 5-dimethylliline (II). There is little doubt that this exists as a resonance hybrid to which the covalent form (II) and the polar form (II*a*) contribute, and moreover that the relative contribution of each form depends on the chemical environment. It is noteworthy that the crystalline keto-amine is yellow, but that its solution in concentrated hydrochloric acid is red, in acetic acid yellow, and in carbon tetrachloride very pale yellow (almost colourless). Since the ionic quinonoid form (II*a*) would undoubtedly be more intensely coloured than the covalent form (II), these results indicate that the proportion of the polar form is greatest in strongly acid media : moreover, it is probable therefore that it is the polar form which unites with acids to give the cation (III). Even so, these salts apparently exist only in strongly acid solution, and are too unstable to exist in the solid state. In these properties the keto-amine (II) strongly resembles both the 1-ketojulolidine and also 1 : 2 : 2*a* : 3 : 4 : 5 : 8 : 9 : 10 : 10*a*-decahydro-5 : 8 -diketo-2*a* : 10*a*-diazapyrene (Almond and Mann, *J.*, 1951, 1906).



(IV)



(V)

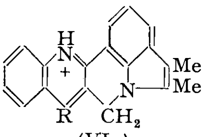


(VI)

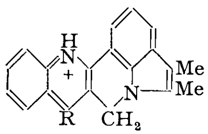
The keto-amine (II) readily formed a phenylhydrazone which in boiling ethanolic hydrogen chloride underwent the Fischer indolisation with the formation of a ψ-indole, *i.e.*, 4 : 5-dimethyl-ψ-indolo(2′ : 3′-1 : 2)liline (IV). The fact that during the reaction two hydrogen atoms have been lost with the formation of a ψ-indole rests on the following evidence : (*a*) the composition of the compound as determined by analysis, which differentiates sharply between the ψ-indole and the true indole, (*b*) infra-red analysis shows no –NH– band in the 3-μ region, which the true indole would of course possess, (*c*) the compound readily forms a stable crystalline hydrochloride, which does show the above –NH– band : this indicates that salt has the structure (V). ψ-Indoles (usually) exhibit this ready salt formation, particularly when (as in V) the process gives an aromatic character to each ring. It should be noted that simple salt formation at the liline nitrogen atom would not produce the above –NH– band. The ψ-indole (IV) also formed a crystalline methiodide, undoubtedly analogous to (V). In these properties the keto-amine (II) strongly resembles 1-ketojulolidine.

When the keto-amine (II) was heated with isatin in alkaline solution, subsequent acidification precipitated 4 : 5-dimethylquinolino(2′ : 3′-1 : 2)liline-4′-carboxylic acid (VI; R = CO_2H), which formed deep red crystals, but gave a bright yellow crystalline potassium salt. The acid (VI; R = CO_2H), when heated in a high vacuum, underwent decarboxylation to give 4 : 5-dimethylquinolino(2′ : 3′-1 : 2)liline (VI; R = H), which also formed bright yellow crystals, but gave a bright red crystalline hydrochloride.

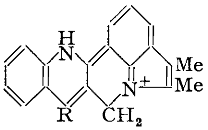
These colour relations indicate strongly that the carboxylic acid (VI; R = CO_2H) must exist as a zwitter-ion, which will have the canonical forms (VI*a*—*c*; R = CO_2^-), and hence would almost certainly be intensely coloured. The anion of the potassium salt could not of course show these forms, and its structure must correspond almost entirely to that of the acid as depicted in (VI; R = CO_2^-) : hence its much paler and less intense colour. The amine (VI; R = H) must also have a structure identical with that of this anion (with of course the CO_2^- group replaced by H), and hence has the same colour as the potassium salt. The hydrochloride of the amine forms a cation which similarly will have three canonical forms corresponding to (VI*a*—*c*; R = H), and hence this hydrochloride has a colour almost identical with that of the free acid in the zwitter-ion form. [It is possible furthermore that some charge separation between nitrogen atoms occurs in the anion of the potassium salt and in the free amine (VI; R = H), the 1′-nitrogen taking a negative and the liline-nitrogen a positive charge; although this may be partly responsible for the pale yellow colour, the separation is probably so small that it can be ignored.] The colour and structural relations of the acid (VI; R = CO_2H) and the base (VI; R = H) and their salts are thus very closely parallel to those of 1 : 2-dihydro-1-phenylquinolino(3′ : 2′-3 : 4)quinoline-4′-carboxylic acid and its decarboxylated base (Mann, *J.*, 1949, 2816).



(VI*a*)

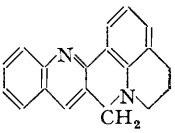


(VI*b*)

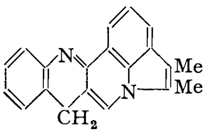


(VI*c*)

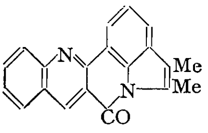
This provides reasonably strong (although indirect) evidence that the structure (VI; R = H) is correctly assigned to the decarboxylated base. The point is important because the structurally similar quinolino(2′ : 3′-1 : 2)juloline (VII) exists in two isomeric forms, one yellow and the other orange, the former giving a deep red, and the latter an orange hydrochloride (Mann and Smith, *loc. cit.*) : interconversion of the two series occurs readily, for the orange base on heating gives the yellow base, whilst the hydrochloride of the yellow base when boiled in aqueous solution is readily transformed into that of the orange base. It was suggested that the difference between the two series was possibly due to allylic tautomerism between the $C_{(3)}$ and the $C_{(4')}$ position.



(VII)



(VIII)



(IX)

It is clear that the liline base (VI; R = H) could theoretically also exist in a similar tautomeric form (VIII) : we have therefore very carefully investigated the properties of the base and its salts, but have not detected any signs of the existence of isomeric forms. The effect of the pyrrole ring is thus to give predominating stability to one of these forms, which is almost certainly that shown as (VI; R = H).

The amine (VI; R = H) showed one marked resemblance to the juloline base (VII) in that, when exposed in benzene solution to the air or when treated with a cold acetone solution of potassium permanganate, it underwent ready oxidation to 3-keto-4 : 5-dimethylquinolino(2′ : 3′-1 : 2)liline (IX). The fact that the base has undergone oxidation in the form (VI; R = H) and not (VIII), *i.e.*, that the keto-group occupies the 3- and not the 4′-position is hardly in doubt, since all previous similar oxidations have thus given rise to cyclic amides. It is noteworthy that the oxidation product (IX) forms cream-coloured crystals, but its hydrochloride is orange. This marked difference in the colour of the hydrochloride of the amine (VI; R = H) and that of the keto-compound (IX) is to be expected, because although the cation of the latter would also have three canonical forms corresponding in type to (VI*a*—*c*; R = H), the form corresponding to (VI*c*; R = H) would now make a much smaller contribution owing to the decrease in basicity of the liline-nitrogen atom caused by the adjoining 3-keto-group : hence this hydrochloride has a much less intense colour than that of the amine (VI; R = H).

We are now investigating the possibility of cyclising 1 : 2-dialkyl-3-2′-cyanoethyl-indoles, and the corresponding 2′-carboxyethyl compounds, in which a similar ring formation should occur at the 4-position.

EXPERIMENTAL.

Many of the following compounds did not give sharp and consistent m. p.s unless the material was heated in an evacuated and sealed capillary tube : all m. p.s so determined are denoted by an asterisk.

1-2′-*Cyanoethyl*-2 : 3-*dimethylindole*.—A mixture of 2 : 3-dimethylindole (50 g.), vinyl cyanide (89 g.), and sodium methoxide (1·8 g.) was heated in an autoclave at 160° for 12 hours, and then distillation furnished the *indole*, b. p. 182—185°/1 mm., which readily solidified and when recrystallised from *cyclo*hexane formed colourless needles, m. p. 80° (39 g., 57%) (Found C, 78·3; H, 7·3; N, 14·0. $C_{13}H_{14}N_2$ requires C, 78·7; H, 7·1; N, 14·1%).

1-2′-*Carboxyethyl*-2 : 3-*dimethylindole*.—The cyano-indole (20 g.) was heated with 10% aqueous potassium hydroxide (300 c.c.) under reflux for 3 hours, and the whole then cooled, filtered, and acidified. The precipitated *acid* recrystallised from aqueous ethanol as colourless crystals which slowly became pink on exposure to light and had m. p. 96—97° (16·8 g., 77%) (Found: C, 71·4; H, 7·1; N, 6·4. $C_{13}H_{15}O_2N$ requires C, 71·8; H, 7·0; N, 6·45%).

1 : 2-*Dihydro*-1-*keto*-4 : 5-*dimethyl-liline* (II).—A mixture of the acid (10 g.), phosphoric anhydride (15 g.), fine silica powder ("Hyflo supercel") (5 g.), and dry xylene (135 c.c.) was heated under reflux for 3 hours with vigorous stirring. The xylene was then decanted, and the residue extracted with boiling xylene (3 × 50 c.c.). The xylene was distilled from the united extracts, and the residue, when recrystallised from light petroleum (b. p. 60—80°), furnished the *keto-amine* (II) as yellow crystals, m. p. 98—99° (3 g., 30%) (Found: C, 78·25; H, 6·3; N, 7·0. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·6; N, 7·0%).

The *phenylhydrazone* readily crystallised when the keto-amine (II) (2 g.), phenylhydrazine (2 g.), acetic acid (1 c.c.), and ethanol (50 c.c.) were boiled together for 3 hours and then cooled: recrystallisation from ethanol gave yellow plates, m. p.* 165—166° (2·2 g., 75%) (Found: C, 79·1; H, 6·8; N, 14·5. $C_{19}H_{19}N_3$ requires C, 78·8; H, 6·6; N, 14·5%). The crystalline hydrazone when set aside slowly decomposed.

4 : 5-*Dimethyl*-ψ-*indolo*(2′ : 3′-1 : 2)*liline* (IV).—Saturated ethanolic hydrogen chloride (15 c.c.) was added to a mixture of the phenylhydrazone (1 g.) and ethanol (15 c.c.) which was then boiled under reflux for 45 minutes, crystals of the hydrochloride of (IV) separating meanwhile. These were collected from the cold mixture and dissolved in hot water, and the solution basified, bright yellow crystals of the ψ-*indolo-liline* (IV) then separating. These crystals (0·47 g., 52%), when recrystallised from methanol, had m. p.* 258° (Found: C, 84·4; H, 5·4; N, 10·4. $C_{19}H_{14}N_2$ requires C, 84·4; H, 5·2; N, 10·4%).

The addition of ethanolic hydrogen chloride to an ethanolic solution of (IV) precipitated the yellow crystalline *hydrochloride* (V), m. p.* 363—365° after recrystallisation from ethanol (Found: C, 74·6; H, 5·2; N, 9·2. $C_{19}H_{14}N_2,HCl$ requires C, 74·4; H, 4·9; N, 9·1%).

When a solution of (IV) in an excess of methanolic methyl iodide was boiled for 3 hours, the orange crystalline *methiodide* was obtained, and after recrystallisation from methanol had m. p.* 362—363° (decomp.) (Found: C, 58·4; H, 4·5; N, 6·8. $C_{20}H_{17}N_2I$ requires C, 58·3; H, 4·2; N, 6·8%).

4 : 5-*Dimethylquinolino*(2′ : 3′-1 : 2)*liline-4′-carboxylic Acid* (VI; R = CO_2H).—A mixture of the keto-amine (II) (2 g.), isatin (2·6 g.), 30% aqueous potassium hydroxide (12 c.c.), and ethanol (50 c.c.) was boiled under reflux under nitrogen for 12 hours. The cold solution was poured into air-free water (150 c.c.) and acidified with 50% aqueous acetic acid. The *acid* was precipitated as a dark red oil which when set aside or (preferably) when heated in water, formed orange-red crystals (3 g., 91%). For purification the acid was dissolved in an excess of hot 20% aqueous potassium hydroxide, giving a yellow solution which on cooling deposited the potassium salt as bright yellow plates, which were recrystallised from 10% potassium hydroxide solution. This salt when treated with aqueous acetic acid deposited the deep red crystalline *hemihydrate*, m. p. 261—262° (effervescence), of the acid (Found: C, 75·0; H, 4·8; N, 8·3. $C_{21}H_{16}O_2N_2,\frac{1}{2}H_2O$ requires C, 74·7; H, 5·1; N, 8·3%). The potassium salt on exposure to damp air readily became red; it was unaffected by boiling methyl iodide.

4 : 5-*Dimethylquinolino*(2′ : 3′-1 : 2)*liline* (VI; R = H).—When the acid (VI; R = CO_2H) (1 g.) was heated at 320°/0·1 mm. for 1 hour, the *amine* sublimed and when then recrystallised from much ethanol formed bright yellow needles, m. p.* 208° (0·7 g., 81%) (Found: C, 84·6; H, 5·6; N, 10·0. $C_{20}H_{16}N_2$ requires C, 84·4; H, 5·7; N, 9·9%).

When ethanolic hydrogen chloride was added to an ethanolic solution of the amine (VI; R = H), the red *hydrochloride* was precipitated; when recrystallised from ethanol this formed bright red needles, m. p.* 302—304° (Found: C, 74·9; H, 5·5; N, 8·65. $C_{20}H_{16}N_2,HCl$ requires C, 74·9; H, 5·3; N, 8·7%).

The formation of this salt under various conditions, and particularly its behaviour when heated with hydrochloric acid and other solvents, were carefully investigated, but no evidence of any change to an isomeric form, similar to that shown by the hydrochloride of quinolino-(2′ : 3′-1 : 2)juloline (VII), could be obtained.

3-*Keto*-4 : 5-*dimethylquinolino*(2′ : 3′-1 : 2)*liline* (IX).—(*a*) A cold acetone solution of potassium permanganate was added with stirring to a solution of the amine (VI; R = H) (0·4 g.) in acetone (200 c.c.) until the latter retained a purple colour. The precipitated manganese dioxide, which contained almost all the oxidation product, was collected and extracted (Soxhlet) with acetone (50 c.c.). The 3-*keto-liline* (IX) separated from the hot acetone, and when cold was collected and recrystallised from 2-methoxyethanol, furnishing very pale yellow (almost cream) needles, m. p.* 251—252° (0·3 g., 71%) (Found: C, 80·6; H, 5·0; N, 9·2. $C_{20}H_{14}ON_2$ requires C, 80·5; H, 4·7; N, 9·4%).

(*b*) A benzene solution of the amine (VI; R = H) was exposed to air for 7 days and then evaporated. Recrystallisation of the residue as before gave pale yellow needles, m. p.* 250—251°, alone and when mixed with the above sample.

The finely powdered amine (VI; R = H) was virtually unaffected by exposure to a stream of air at 120° for 10 hours.

When ethanolic hydrogen chloride was added to a cold acetone solution of (IX), the *hydrochloride* was precipitated as orange crystals which had m. p.* 251° and hence had apparently completely dissociated before reaching the m. p. of the base (Found: C, 71·8; H, 4·8; N, 8·35. $C_{20}H_{14}ON_2,HCl$ requires C, 71·8; H, 4·5; N, 8·4%).

We are greatly indebted to Dr. R. N. Haszeldine for the spectroscopic investigation, to the Department of Scientific and Industrial Research for a grant (to C. Y. A.), and to Imperial Chemical Industries Limited, Dyestuffs Division, for the gift of various compounds.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, January 22nd,* 1952.]