

The Structure and Properties of Certain Polycyclic Indolo- and Quinolino-derivatives. Part VII. Derivatives of 1:6-Dioxojulolidine.†*

By JOHN T. BRAUNHOLTZ and FREDERICK G. MANN.

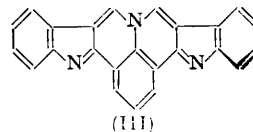
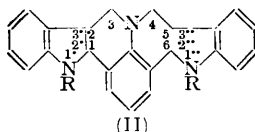
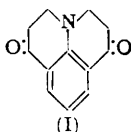
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The bisphenyl- and bisdiphenyl-hydrazone of 1:6-dioxojulolidine undergo the Fischer indolisation to furnish the corresponding di-indolo-julines; the first of these is stable only as its salts. ψ -Indole formation was not observed in this series.

1:6-Dioxojulolidine, when submitted to the Pfitzinger reaction with isatin, gives the purple diquinolinojulinedicarboxylic acid (IV), which on heating undergoes the allylic rearrangement to the orange isomeric acid (V). The latter on decarboxylation gives the orange diquinolino-juline (VI), which when heated with hydrochloric acid shows the same rearrangement, with formation of the isomeric red base (VII); sublimation reconverts (VII) into (VI).

AN examination has been made, on closely similar lines to the work described in Part VI,* of the product obtained when (a) the bisphenylhydrazone of 1:6-dioxojulolidine (I) is subjected to the Fischer indolisation, and (b) the base (I) is condensed by the Pfitzinger reaction with isatin in alkaline solution. The possible isomerisation of the products obtained by the Pfitzinger reaction has also been studied, but the far greater insolubility of these products and their duplication of chemical function has prevented so exhaustive a study of their derivatives as that on the products described in Part VI.

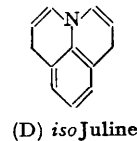
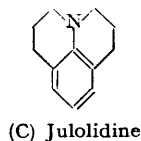
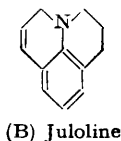
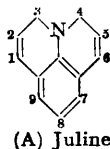
When a solution of the bisphenylhydrazone of 1:6-dioxojulolidine (I) in ethanolic hydrogen chloride was boiled, the initial deep purple colour slowly faded to orange, and the highly crystalline orange monohydrochloride of di-indolo(2':3'-1:2)(3''-2''-5:6)juline



(II; R = H) separated; this salt was converted into the crystalline orange monohydride, thiocyanate, and picrate, and it is clear that in these compounds salt formation (as expected) has occurred on the central nitrogen atom. Treatment of a solution of the hydrochloride with aqueous sodium hydroxide precipitated the di-indolo-compound (II; R = H) as a lemon-yellow flocculent mass, which on exposure to light and air underwent rapid darkening, so that purification and spectroscopic examination were not possible. In view of the results obtained with 1-oxojulolidine (Mann and Smith, *J.*, 1951, 1898), and with 1:2:3:4-tetrahydro-4-oxo-1-phenylquinoline (Mann, *J.*, 1949, 2816) and its 1-methyl analogue (Part VI), it might have been expected that the above indolisation would have been accompanied by dehydrogenation and the formation of the dehydro-derivative (III). Evidence that salts of the true indole (II; R = H) have been formed is provided by analysis, and by the strong probability, based on previous examples, that the colour of a ψ -indole such as (III) would be markedly more intense than that of its salts. Furthermore, the indolisation of the bisdiphenylhydrazone of (I) similarly gave

* Part VI, preceding paper.

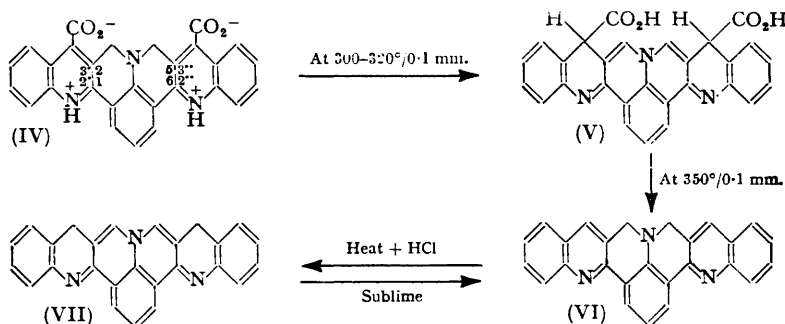
† In Part II (*J.*, 1951, 1898), following the Editor's advice, the bases (A), (B), and (C) were named as below: we now suggest the name *isojuline* for (D).



the orange crystalline monohydrochloride of 1': 1''-diphenyldi-indolo(2': 3'-1 : 2)(3'' : 2''-5 : 6)juline (II; R = Ph); in this case the pure di-indolo-compound (II; R = Ph) could be isolated, but it rapidly decomposed when in contact with organic solvents.

The reason why in this series the true indole (II), and not the ψ -indole (III), is formed remains uncertain. It may be significant that the ψ -indoles previously described have been strong anhydronium bases, giving stable salts in which the whole cation had become fully aromatic in structure: this process would not be possible in (III) because of the central nitrogen atom.

When a solution of the diketone (I) and isatin in aqueous methanolic sodium hydroxide was boiled for twenty hours, filtration of the orange liquid into dilute acetic acid caused deposition of fine deep purple crystals of diquinolino(2': 3'-1 : 2)(3'' : 2''-5 : 6)juline-4': 4''-dicarboxylic acid (IV). The evidence for the zwitterion structure (IV) is: (i) This resonance structure would receive contributions from numerous canonical forms, in which any two of the three nitrogen atoms can accept the protons; hence it would certainly be intensely coloured. (ii) The acid dissolves in hydrochloric acid to give a blackish-purple solution, but dissolves in sodium hydroxide to give an orange solution and ultimately a hygroscopic crystalline yellow salt; clearly the hydrochloric acid would convert the $\cdot\text{CO}_2^-$ ions in (IV) into $\cdot\text{CO}_2\text{H}$ groups, without affecting the fundamental structure or colour, whereas alkalis would remove the proton from the nitrogen atoms in (IV) and thus destroy resonance of the above type. (iii) The infra-red spectrum of (IV) is ill-defined in the $3\text{-}\mu$ region, with peaks at 2.95 and 3.13μ , but two strong bands appear at 6.20 and 6.35μ , the latter being the stronger and sharper. Amino-acids having a zwitterion structure usually have a band at $6.11\text{--}6.21 \mu$ and a stronger one at $6.21\text{--}6.38 \mu$. The peaks in the $3\text{-}\mu$ region and the band at 6.35μ in the spectrum of (IV) can therefore be ascribed to the $\equiv\text{NH}^+$ and the $\cdot\text{CO}_2^-$ groups, respectively.



The acid (IV) was recovered unchanged after several hours' boiling with hydrochloric acid. When, however, the powdered acid was cautiously heated to $300\text{--}320^\circ/0.1 \text{ mm.}$, *i.e.*, well below its decomposition temperature, it became bright orange without change in composition. This transformation is apparently due to "allylic rearrangement" (cf. Part VI) and the consequent formation of 4': 4''-dihydrodiquinolino(2': 3'-1 : 2)(3'' : 2''-5 : 6)isojuline-4': 4''-dicarboxylic acid (V). The evidence for this structure is: (i) The acid (V) dissolves in aqueous sodium hydroxide solution to give a yellow solution, the ultra-violet spectrum of which is markedly different from that of a similar solution of the acid (IV) (p. 397); the two acids are therefore structurally distinct. (ii) The alkaline solution of (V) when poured into an excess of acetic acid gives a blood-red colour markedly different from the intense purple colour which the acid (IV) shows under these conditions; proton addition to the 1': 1''-nitrogen atoms in (V) would give a cation showing a resonance similar to that of (IV) but involving fewer quinonoid rings and hence presumably causing less intense colour. The infra-red spectrum is also ill-defined in the $3\text{-}\mu$ region, with peaks at 3.02μ and 3.12μ , but shows a single strong band at 6.35μ ; the weaker band at $6.11\text{--}6.21 \mu$ shown by amino-acids is apparently indicated only as a faint shoulder at 6.20μ whereas the band at 5.85μ shown by un-ionised carboxylic acids is absent. The position of the protons in the acid (V) is therefore uncertain: the infra-red evidence on

the whole indicates a zwitterion structure, which is not supported by the marked colour change caused by acidification. The apparent contradiction may be due to intermolecular hydrogen bonding or (less probably) to some influence exerted by the central nitrogen atom. The spectroscopic evidence however places the structural difference of the acids (IV) and (V) beyond doubt.

Although the allylic rearrangement in compounds of this general type is usually promoted by hot acids, the above thermal transformation is strictly comparable to that of 1:2-dihydroquinolino(3':2'-3:4)quinoline-4'-carboxylic acid (Part VI, *loc. cit.*).

The acid (IV), when more vigorously heated under reduced pressure, was first converted into the acid (V), which then underwent decarboxylation and gave a crystalline orange sublimate. This dissolved in hot pyridine to form an orange solution which had a vivid yellow fluorescence, and which on cooling deposited diquinolino(2':3'-1:2)(3'':2''-5:6)juline (VI) in deep orange needles, m. p. 319°. This base dissolved in hot concentrated

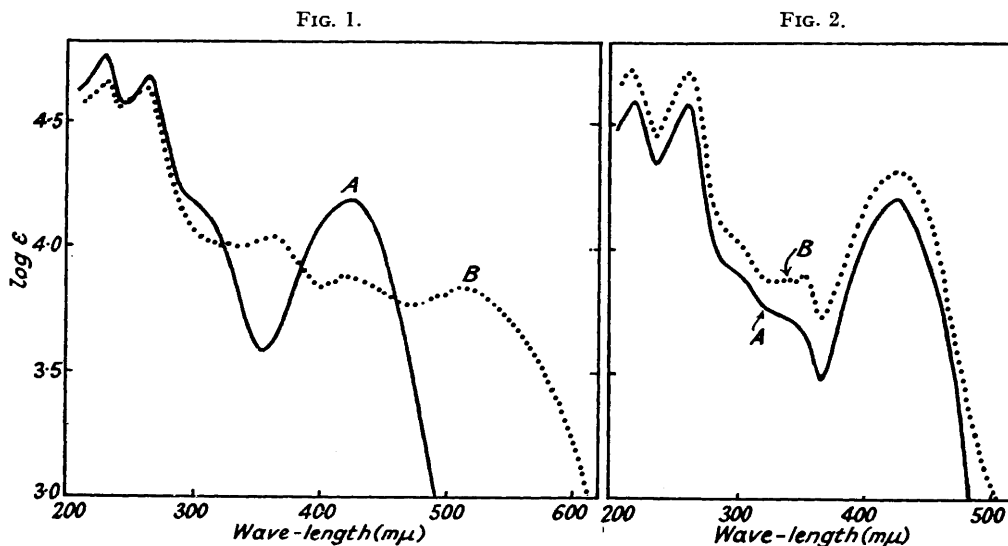


FIG. 1. *Di*quinolino(2':3'-1:2)(3'':2''-5:6)juline (VI), (A) in methanol (1.20 mg./250 c.c.); (B) in methanol (1.30 mg./200 c.c.) containing 0.25 c.c. of 3N-HCl.

FIG. 2. 4':4''-Dihydrodiquinolino(2':3'-1:2)(3'':2''-5:6)isojuline (VII), (A) in methanol (0.77 mg./50 c.c.); (B) in methanol (0.77 mg./50 c.c.) containing 0.30 c.c. of 3N-HCl.

hydrochloric acid to form a purple solution very similar in colour to a solution of the acid (IV); this solution deposited purple crystals of a hydrochloride, stable only in presence of hydrochloric acid. The purple colour indicates that the cation of the hydrochloride has the same essential structure as (IV), with of course the $\cdot\text{CO}_2^-$ groups replaced by hydrogen atoms; this cation will therefore show similar resonance. This is confirmed by the ultra-violet absorption spectra (Fig. 1) of the base (VI) in methanol and in methanolic hydrochloric acid: the marked difference in these spectra demonstrates the considerable (resonance) difference in the base and its hydrochloride.

It is clear therefore that heating the acid (IV) involves the allylic rearrangement to (V), with a reversal of this process as the decarboxylated product volatilises (see below).

When the purple solution of the base (VI) in concentrated hydrochloric acid was boiled under reflux, a very slow colour change occurred, and ultimately the solution became deep reddish-brown and a brown crystalline hydrochloride separated. This salt was also unstable in the absence of an excess of acid, but when treated with aqueous sodium hydroxide gave an isomeric base (VII), which crystallised from pyridine in dark red needles, m. p. 319°, alone or when mixed with (VI).

The fact that the bases (VI) and (VII) are isomeric and are not dimorphic forms of the same compound is based on the following evidence. (i) The deep orange and the deep

red colour of the bases, shown by crystals of approximately the same size, is retained when the crystals are very finely ground; the colours are thus the true colours of the bases and are not due to surface reflexion (cf. Part VI). (ii) The base (VII) in hot pyridine gives a deep red solution with a faint orange-red fluorescence, and in warm concentrated hydrochloric acid a pale yellowish-brown solution. (iii) The ultra-violet absorption spectra of (VII) in methanol and in methanolic hydrochloric acid (Fig. 2) are closely similar, indicating that salt formation has made no significant change in the structure. (iv) The infra-red spectra of (VI) and (VII) are unlike (p. 397).

It is therefore almost certain that the hydrochloric acid has again caused the allylic rearrangement, and that the dark red base is 4': 4''-dihydrodiquinolono(2': 3'-1 : 2)(3'' : 2''-5 : 6)isojuline (VII), and that salt formation occurs solely on the central nitrogen atom. There is of course no evidence as to whether the allylic rearrangement occurs on one or both sides of the molecule, and the symmetric double rearrangement has been assumed; this is the logical conclusion if the mechanism suggested in Part VI is correct.

When the red base (VII) was heated at 280—300°/0.1 mm., it sublimed smoothly with conversion into the crystalline orange base (VI), the identity of which was fully established by its properties. The fact that the two bases have the same m. p. and mixed m. p. indicates that this conversion occurs at or before this temperature; further, it is highly probable that decarboxylation of the acid (V) gives rise initially to (VII) which is then immediately transformed into (VI).

It is noteworthy that the three pairs of isomeric bases which have arisen in this series (cf. Parts II and VI) show certain constant features, namely, the second isomer is darker than the first, and the conversion of the first into the second is promoted by acid treatment, and reversed by heat.

Atmospheric oxidation of the bases (VI) and (VII) in benzene solution, which was a characteristic property of the two earlier and comparable isomeric pairs, could not be determined because of their very low solubility; no such oxidation could be detected in the solid state or in hot pyridine solution. Oxidation with potassium permanganate also could not be investigated owing to the negligible solubility of (VI) and (VII) in suitable solvents.

An apparently similar example of isomerism has been briefly recorded by Clemo and Johnson (*J.*, 1930, 2133), who found that 5': 6'-dimethoxyindeno(2': 3'-3 : 4)quinoline occurred in a pale yellow and a reddish-brown form, having identical m. p.s. alone and mixed. Since, however, the form obtained depended on the solvent employed for crystallisation, and the fluorescent properties of their solutions were apparently identical, dimorphism cannot be excluded.

EXPERIMENTAL

M. p.s, unless otherwise recorded, were determined in evacuated sealed tubes, which were immersed at 10—15° below the m. p.

Di-indolo(2': 3'-1 : 2)(3'' : 2''-5 : 6)juline (II; R = H).—The bisphenylhydrazone of 1 : 6-dioxojulolidine (1 g.) (Mann and Smith, *loc. cit.*) was dissolved in saturated ethanolic hydrogen chloride (40 c.c.), to which ethanol (10 c.c.) had been added, and the purple solution boiled under reflux for 5 hr., its colour changing meanwhile to orange and crystals being deposited. It was set aside overnight, and the orange crystalline monohydrated *monohydrochloride* of the di-indolojuline (II; R = H), when then collected and thoroughly washed with warm water, had m. p. 346° (decomp.) (yield, 0.6 g., 57%) (Found: C, 71.8; H, 4.8; N, 10.6. $C_{24}H_{17}N_3.HCl.H_2O$ requires C, 71.75; H, 5.0; N, 10.45%). The salt is too insoluble for recrystallisation.

A solution of the hydrochloride in boiling methanol, when added to a similar solution of sodium iodide, precipitated the *monohydriodide*, m. p. above 400° (Found: C, 60.5; H, 3.5; N, 8.65. $C_{24}H_{17}N_3.HI$ requires C, 60.65; H, 3.8; N, 8.85%). The *thiocyanate*, similarly prepared by using potassium thiocyanate, formed a microcrystalline powder, m. p. 318° (decomp.) (Found: C, 73.6; H, 4.3; N, 13.6. $C_{24}H_{17}N_3.HCNS$ requires C, 73.85; H, 4.45; N, 13.8%). The *monopicrate* had m. p. 253° (decomp.) (Found: C, 62.3; H, 3.35; N, 14.3. $C_{24}H_{17}N_3.C_6H_5O_7.N_3$ requires C, 62.5; H, 3.5; N, 14.55%). All these salts separated as bright orange crystals.

A solution of the monohydrochloride in much boiling aqueous methanol was filtered into an

excess of 10% aqueous sodium hydroxide, and the precipitated lemon-yellow base (II; R = H) collected and washed as rapidly as possible. Its colour began to deepen almost immediately when it was exposed to light and to air, and more slowly in a vacuum. The base recrystallised from acetone-ethanol as yellow platelets, but these could not be isolated free from the decomposition product.

1' : 1''-Diphenyl-di-indolo(2' : 3'-1 : 2)(3'' : 2''-5 : 6)juline (II; R = Ph).—The bisdiphenyl-hydrazone of (I) (Braunholtz and Mann, *J.*, 1953, 1823), when treated as above, also ultimately gave a pale orange solution containing ammonium chloride crystals. The filtered solution, when concentrated, diluted with water, and set aside overnight, deposited the *monohydrochloride* of the juline (II; R = Ph), bright orange crystals, m. p. 260° (decomp.), from aqueous ethanol (Found : C, 80.8; H, 5.3; N, 7.75. $C_{38}H_{28}N_3 \cdot HCl$ requires C, 80.65; H, 4.9; N, 7.8%). This salt when added to aqueous sodium hydroxide (as above) precipitated the *juline* (II; R = Ph), which when thoroughly washed with water and ethanol and dried at 65°/0.1 mm. formed a mustard-coloured amorphous powder, m. p. 170° (decomp.) (Found : N, 8.5. $C_{38}H_{28}N_3$ requires N, 8.4%). The base, when heated at 0.01 mm., underwent fusion and then charring, without detectable sublimation. It was sparingly soluble in hot ethanol and acetone, far more soluble in benzene and pyridine, but all such solutions rapidly darkened in colour as decomposition ensued, and crystallisation was not achieved.

Diquinolino(2' : 3'-1 : 2)(3'' : 2''-5 : 6)*juline-4' : 4''-dicarboxylic Acid* (IV).—The diketone (I) (2 g.) was added to a solution of isatin (3 g.) and potassium hydroxide (3.6 g.) in methanol (25 c.c.) and water (5 c.c.), which was then boiled under reflux for 20 hr., cooled, and filtered into an excess of 10% acetic acid. The precipitated purple acid (IV), when collected, washed with much ethanol and water, and dried in a vacuum, had m. p. 363° (decomp., with preliminary change in colour to orange) (4 g., 87%). The acid is hygroscopic, and before analysis was exposed to air until the stable *tetrahydrate* had been formed (Found : C, 63.2; H, 4.9; N, 7.65. $C_{28}H_{17}O_4N_3 \cdot 4H_2O$ requires C, 63.2; H, 4.7; N, 7.9%).

The acid dissolved readily in warm aqueous sodium hydroxide or carbonate, and the orange solution on cooling deposited the crystalline orange sodium salt, which was too deliquescent for isolation in the pure state. Acidification of the solution with acetic acid changed the colour immediately to purple, and the crystalline acid (IV) slowly separated.

The ultra-violet absorption spectrum of the acid (IV) in 10% aqueous sodium hydroxide showed the characteristics :

$\lambda_{max.}$...	390—393	266	229—231	$\lambda_{min.}$...	356	252	224	$\lambda_{inf.}$...	300—308
$\epsilon_{max.}$...	10,950	46,600	58,900	$\epsilon_{min.}$...	7050	40,800	56,000	$\epsilon_{inf.}$...	14,600

4' : 4''-Dihydroquinolino(2' : 3'-1 : 2)(3'' : 2''-5 : 6)*isojuline-4' : 4''-dicarboxylic Acid* (V).—The finely powdered acid (IV) was cautiously heated at 300—320°/0.1 mm. until conversion into the orange acid (V) was complete. This acid is also hygroscopic, and when exposed to the air for 12 hr. became brown, the change being reversed by gentle warming under reduced pressure. A sample of the freshly prepared acid, exposed to the air but analysed before the onset of darkening, had formed a *sesquihydrate* (Found : C, 68.9; H, 4.3; N, 8.9. $C_{28}H_{17}O_4N_3 \cdot 1.5H_2O$ requires C, 69.2; H, 4.15; N, 8.65%). The anhydrous acid had m. p. 363° (decomp.), showing that in a normal m. p. determination the conversion (IV) \rightarrow (V) is complete before fusion.

A solution of (V) in aqueous 10% sodium hydroxide was too dilute for accurate determination of ϵ values, but showed the characteristics : $\lambda_{max.}$ 424—428, $\lambda_{min.}$ 412—414, $\lambda_{inf.}$ 438—456, 376—388.

Diquinolino(2' : 3'-1 : 2)(3'' : 2''-5 : 6)*juline* (VI).—The preparation of this compound was best carried out by heating the purple acid (IV) in a cold-finger sublimation apparatus, at first gently at 15 mm. to ensure dehydration and conversion into (V) and then in a metal-bath at ca. 350°/0.1 mm.; decarboxylation then occurred with deposition of a crystalline sublimate, which was yellow to orange according to the particle size. The sublimate, recrystallised from pyridine, gave the *juline* (VI), lustrous deep orange needles, m. p. 319.5° (decomp.) (Found : C, 84.3; H, 4.7; N, 11.15. $C_{28}H_{17}N_3$ requires C, 84.1; H, 4.6; N, 11.3%); the low yield (50%) was due to extensive charring at the decarboxylation temperature.

The infra-red spectrum of (VI) shows in particular a sharp band at 6.23 μ flanked by weaker bands at 6.15 and 6.33 μ , and a strong single band at 13.55 μ .

The purple solution of the juline (VI) in hot concentrated hydrochloric acid, on cooling, deposited an unstable deep bluish-purple crystalline hydrochloride, which when collected and washed with water became red and finally yellow; this colour change also occurred when the hydrochloride, after being washed with hydrochloric acid, was dried in a vacuum.

4 : 4''-Dihydroquinolino(2' : 3'-1 : 2)(3'' : 2''-5 : 6)isojuline (VII).—A solution of the base (VI) in concentrated hydrochloric acid was boiled under reflux for 4 hr., the deep purple colour becoming slowly reddish and finally yellowish-brown, and a reddish-brown crystalline hydrochloride separating from the boiling solution. A sample of this hydrochloride when collected and exposed to the air became olive-green and when warmed with water became yellowish-brown; purification was therefore not attempted. When the cold reaction mixture was treated with aqueous sodium hydroxide, the particles of the hydrochloride became at first yellowish and then dull red. The crude base, when collected and recrystallised from pyridine, furnished the isojuline (VII) as lustrous deep red needles, m. p. 319° (Found : C, 83.9; H, 4.9; N, 11.5. $C_{28}H_{17}N_3$ requires C, 84.1; H, 4.6; N, 11.3%); the yield was almost quantitative.

The main features of the infra-red spectrum of (VII) are bands at 6.07, 6.15, and 6.25 μ (of strength, 6.07 > 6.25 > 6.15) and a strong broad-based band at 13.38 μ flanked by weaker bands at 13.1 and 13.8 μ (cf. VI).

Conversion of the Base (VII) into the Isomer (VI).—The red base (VII) (150 mg.), when heated in a small sublimation apparatus at 280—300°/0.1 mm., gave the beautifully crystalline deep orange base (VI) (140—150 mg.), which was identified by its m. p., infra-red spectrum, and the colour of solutions in organic solvents and in hydrochloric acid.

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