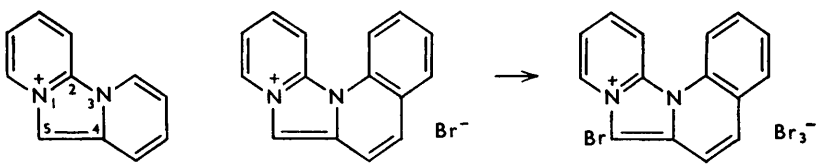
305. *Polynuclear Heterocyclic Systems. Part II.* Substitution Reactions of Condensed Glyoxalinium Salts.*

By B. R. Brown and D. White.

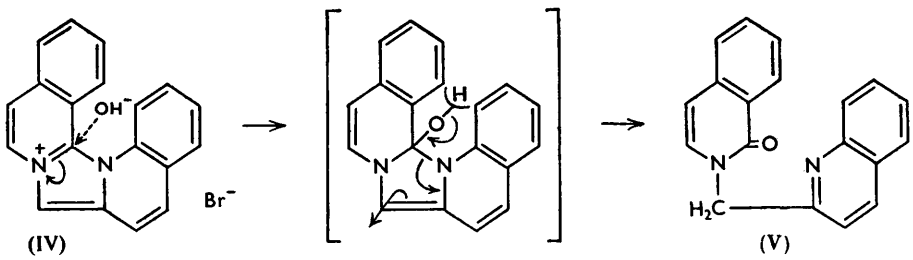
Bromination of pyridino(1′ : 2′-1 : 2)quinolino(1″ : 2″-3 : 4)glyoxalinium and diquinolino(1′ : 2′-1 : 2, 1″ : 2″-3 : 4)glyoxalinium salts has yielded compounds substituted in the 5-position. Sodium hydroxide disrupts the nucleus of diquinolinoglyoxalinium and quinolino(1′ : 2′-3 : 4)*iso*quinolino-(1″ : 2″-2 : 1)glyoxalinium salts with formation of *N*-2-quinolylmethyl-carbostyril and -*iso*carbostyril respectively.

Consideration of the possible electronic shifts in the parent dipyridinoglyoxalinium cation (I) leads to the conclusion that substitution in the nucleus by cationoid reagents will occur at the 5-position, and that attack by anionoid reagents is favoured at the 2-position among others. The addition of further benzene nuclei, as in pyridinoquinolino-glyoxalinium (II), diquinolinoglyoxalinium, and quinolino*iso*quinolinoglyoxalinium salts (IV), does not alter the predictions.



(I) (II) (III)

Bromination of pyridinoquinolinoglyoxalinium bromide (II) in aqueous acetic acid affords 5-bromopyridinoquinolinoglyoxalinium perbromide (III) whose identity was proved by comparison with the compound synthesised as described in Part I.* Similarly, bromination of diquinolinoglyoxalinium perchlorate produces the 5-bromo-perbromide, which, for comparison, has been synthesised by one of the general methods previously described (Part I).



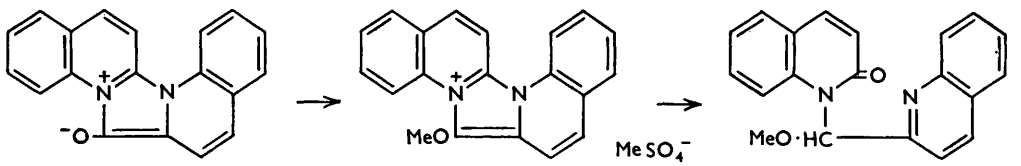
(IV) (V)

Aqueous sodium hydroxide, an anionoid reagent, destroys the nucleus, and the structure of the product confirms the glyoxalinium structures assigned to these compounds. Quinolino(1′ : 2′-3 : 4)*iso*quinolino(1″ : 2″-2 : 1)glyoxalinium bromide (IV) (synthesised by the standard method) yields *N*-2-quinolylmethyl*iso*carbostyril (V), whose structure has been confirmed by synthesis from *iso*carbostyril and ω-bromoquinaldine in the presence of methanolic potassium hydroxide.[1] Diquinolinoglyoxalinium bromide yields a compound which, from its ultraviolet and infrared spectra and by analogy with the reaction of quinolino*iso*quinolinoglyoxalinium bromide, must be *N*-2-quinolylmethyl-carbostyril though attempts to synthesise this from ω-bromoquinaldine and carbostyril

* Part I, *J.*, 1956, 1158.

[1] Cf. Fernau, *Monatsh.*, 1893, **14**, 59.

failed (only starting materials or ωω-dibromoquinaldine, produced by disproportionation of the monobromo-compound,[2] has been isolated). Elucidation of the action of sodium hydroxide on glyoxalinium salts enables the formula (VII) to be assigned to the product obtained by Krollpfeiffer and Schneider[3] from Besthorn's Red (VI) by the action of methyl sulphate and alkali.



(VI) (VII)

Experimental

Pyridino(1′ : 2′-1 : 2)*quinolino*(1″ : 2″-3 : 4)*glyoxalinium Series.—Bromination of pyridinoquinolinoglyoxalinium bromide.* Pyridinoquinolinoglyoxalinium bromide (II) (0·90 g.) was dissolved in acetic acid (20 ml.) containing a few drops of water. Bromine (1·2 ml.) in acetic acid (10 ml.) was added gradually at 90° until bromine was in excess. The mixture was kept at 90° for 30 min., then cooled, and the yellow solid separated and washed with acetic acid and ether. Recrystallisation from acetic acid yielded yellow plates (0·75 g.) (Found: C, 33·8; H, 2·2. Calc. for $C_{15}H_{10}N_2Br_4$: C, 33·5; H, 1·85%). The infrared spectrum of the compound was identical with that of 5-bromopyridino(1′ : 2′-1 : 2)quinolino(1″ : 2″-3 : 4)glyoxalinium perbromide (Part I).

Treatment of this perbromide with pyridine yielded 5-bromopyridinoquinolinoglyoxalinium bromide which separated from methanol as pale yellow needles (Found: C, 47·8; H, 2·65. Calc. for $C_{15}H_{10}N_2Br_2$: C, 47·6; H, 2·65%). Infrared comparison proved the identity of the compound.

Diquinolino(1′ : 2′-1 : 2, 1″ : 2″-3 : 4)*glyoxalinium Series.—Bromination of diquinolinoglyoxalinium perchlorate.* Diquinolinoglyoxalinium perchlorate (0·90 g.) in aqueous acetic acid (80 ml.) was treated gradually with bromine in acetic acid at 90° until, after about 10 min., bromine was in slight excess and a permanent yellow precipitate had been produced. The mixture was cooled, and the solid collected, washed, and recrystallised from acetic acid to yield *5-bromodiquinolino*(1′ : 2′-1 : 2, 1″ : 2″-3 : 4)*glyoxalinium perbromide* (0·90 g.) as pale yellow needles (Found: C, 38·8; H, 2·15; N, 4·6; Br, 54·3. $C_{19}H_{12}N_2Br_4$ requires C, 38·7; H, 2·05; N, 4·75; Br, 54·4%).

5-Bromodiquinolino(1′ : 2′-1 : 2, 1″ : 2″-3 : 4)*glyoxalinium bromide.* The above perbromide (0·90 g.) was treated with just insufficient pyridine (about 6 ml.) to dissolve it. The mixture was swirled vigorously and the colourless solution was filtered from the remaining solid. Overnight the solution became brown and yellow crystals were deposited. These were washed with ether and recrystallised twice from methanol–ether to yield yellow needles (0·20 g.) of the *bromide* (Found: C, 52·6; H, 3·05. $C_{19}H_{12}N_2Br_2,\frac{1}{2}CH_4O$ requires C, 52·7; H, 3·15%). The infrared spectrum of the compound contains a band at 3425 cm.$^{-1}$ characteristic of the solvent of crystallisation. The *perchlorate* prepared in water and crystallised from ethanol formed yellow-brown prisms (Found: C, 51·5; H, 2·75. $C_{19}H_{12}O_4N_2ClBr$ requires C, 51·0; H, 2·7%).

5-Bromodiquinolino(1′ : 2′-1 : 2, 1″ : 2″-3 : 4)*glyoxalinium perbromide.* 1-2′-Quinolylmethylquinolinium bromide[4] (0·20 g.), acetic acid (5·0 ml.), water (10 ml.), and sodium acetate (0·5 g.) were heated at 90° and treated dropwise with bromine in acetic acid until no further precipitation was observed. The yellow crystals were separated from the cold mixture, washed with acetic acid, and crystallised from acetic acid to yield yellow needles (0·11 g.) (Found: N, 4·55. Calc. for $C_{19}H_{12}N_2Br_4$: N, 4·75%). Infrared comparison showed the compound to be identical

[2] Brown, Grice, Hammick, and Thewlis, *J.*, 1951, 1149.
[3] Krollpfeiffer and Schneider, *Annalen*, 1937, **530**, 34.
[4] Hammick, Lammiman, Morgan, and Roe, *J.*, 1955, 2440.

with that prepared by the bromination of diquinolinoglyoxalinium perchlorate as described above.

Action of sodium hydroxide on diquinolinoglyoxalinium bromide. Diquinolinoglyoxalinium bromide (0·20 g.) was boiled under reflux for 30 min. with 10% sodium hydroxide solution (30 ml.). An oil separated which solidified in the cold. Extraction with chloroform yielded a solid which separated from light petroleum (b. p. 60—80°) as colourless needles, m. p. 125° (Found, in material dried at 80° in high vacuum for 3 hr.: C, 79·35; H, 5·0. $C_{19}H_{14}ON_2$ requires C, 79·7; H, 4·9%). Light absorption in EtOH: max. at 270, 303, 308, 316, and 330 mμ (log ε 4·00, 3·77, 3·77, 3·93, and 3·76); min. at 295, 306, 312, and 322 mμ (log ε 3·63, 3·72, 3·73, and 3·74). The *picrate* separated from methanol as yellow needles, m. p. 189° with previous softening (Found: C, 56·8; H, 3·9. $C_{25}H_{17}O_8N_5,CH_4O$ requires C, 57·0; H, 3·8%).

Quinolino(1′ : 2′-3 : 4)iso*quinolino*(1″ : 2″-2 : 1)*glyoxalinium Series.—Quinolino*iso*quinolinoglyoxalinium perchlorate.* A solution of ωω-dibromoquinaldine (5·0 g.) in *iso*quinoline (40 ml.) was boiled under reflux for 4 hr. The mixture was cooled to about 30° and ether was added to prevent solidification of unused *iso*quinoline. Overnight dark crystals appeared and these were separated by decantation and well washed with ether. This solid was treated with charcoal in boiling water, to yield a clear yellow solution which deposited a red oil in the cold. The liquid was decanted from the oil, and sodium hydroxide solution was added until the solution was just alkaline to litmus. Several extractions with ether removed the liberated *iso*quinoline. The resulting solution was heated to expel ether and filtered.

To one-third of the filtrate excess of aqueous perchloric acid was added and the precipitated solid was collected, washed with water, and crystallised twice from methanol, to yield *quinolino*(1′ : 2′-3 : 4)iso*quinolino*(1″ : 2″-2 : 1)*glyoxalinium perchlorate* as pale yellow needles (Found: C, 61·8; H, 3·7. $C_{19}H_{13}O_4N_2Cl$ requires C, 61·9; H, 3·5%). Light absorption in EtOH: max. at 284, 295, 362, and 380 mμ (log ε 4·41, 4·36, 4·07, and 4·03); min. at 254, 292, 323, and 373 mμ (log ε 4·00, 4·34, 3·65, and 3·98).

To another third of the above filtrate was added aqueous hydrobromic acid until the solution was just acid to litmus, and then excess of hot aqueous picric acid. In the cold a yellow solid was precipitated which was separated, washed with water, and twice recrystallised from methanol to yield the *picrate* (0·80 g.) as yellow needles, m. p. 234° (Found: C, 60·0; H, 3·0. $C_{25}H_{15}O_7N_5$ requires C, 60·35; H, 3·0%).

*Action of sodium hydroxide on quinolino*iso*quinolinoglyoxalinium bromide.* To the remaining third of the above filtrate was added concentrated sodium hydroxide solution (to *ca.* 10% NaOH), and the mixture was boiled for 10 min. A white crystalline solid was produced and more separated in the cold. This solid was collected, dried, and crystallised twice from light petroleum (b. p. 60—80°) to yield colourless needles (1·1 g.), m. p. 138° (Found, in material dried at 110° in a high vacuum: C, 79·6; H, 5·1; N, 9·7. $C_{19}H_{14}ON_2$ requires C, 79·7; H, 4·9; N, 9·8%). The compound is hygroscopic. Light absorption in EtOH: max. at 234, 280, 303, 309, and 316·5 mμ (log ε 4·83, 4·13, 3·91, 3·83, and 3·98); min. at 256, 300, 307, and 312·5 mμ (log ε 3·83, 3·86, 3·81, and 3·80). The m. p. of the compound was unchanged on admixture with a sample of 2-2′-quinolylmethyl*iso*carbostyril synthesised as described below, and the ultraviolet and infrared spectra of the two were identical.

The action of aqueous sodium hydroxide on quinolino*iso*quinolinoglyoxalinium picrate yielded the same compound, m. p. 138°.

The *picrate* was prepared in methanol and recrystallised from acetone–ether as yellow needles, m. p. 214° (Found: C, 57·75; H, 3·4. $C_{25}H_{17}O_8N_5$ requires C, 58·25; H, 3·3%).

iso*Carbostyril acetate.* *iso*Quinoline *N*-oxide (5·8 g.) and acetic anhydride (100 ml.) were boiled under reflux for 5 hr. and the mixture was poured into ice and water. The brown crystals which separated (5·4 g.) were washed with water, dried, and recrystallised several times from light petroleum (b. p. 60—80°), to yield iso*carbostyril acetate* as colourless prismatic needles, m. p. 89° (Found: C, 70·9; H, 4·95. $C_{11}H_9O_2N$ requires C, 70·6; H, 4·8%). The mother-liquors of the above crystallisations yielded colourless needles of *iso*carbostyril produced by hydrolysis of some of the acetate when the reaction mixture was poured into water.

iso*Carbostyril.* *iso*Carbostyril acetate (1·0 g.) was dissolved in 10% aqueous hydrochloric acid (40 ml.) and the solution was kept at 80° for 30 min., cooled, and treated with solid sodium carbonate until alkaline. The precipitated solid was separated, washed with water, dried, and recrystallised from acetone, to yield *iso*carbostyril (0·40 g.) as colourless needles, m. p. 214°.

2-2′-*Quinolylmethyl*iso*carbostyril.* A solution of ω-bromoquinaldine (0·40 g.), *iso*carbostyril

(0·30 g.), and potassium hydroxide (0·1 g.) in methanol (25 ml.) was boiled under reflux for 2 hr., then poured into water, and the resulting white precipitate was collected, washed with water, dried, and recrystallised from light petroleum (b. p. 60—80°) to yield 2-2′-quinolylmethyl*iso*carbostyril (0·25 g.) as needles, m. p. 138° (Found: N, 9·7. Calc. for $C_{19}H_{14}ON_2$: N, 9·8%).

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, November 30th*, 1956.]