800. *A Novel Reaction of the Pyridine Ring.*

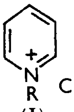
By G. E. Ficken and J. D. Kendall.

The preparation of 2-chloro-3,3-dimethylindolenine from 3,3-dimethyloxindole is described. The chloroindolenine, when treated in pyridine with a 2-methylbenzothiazole quaternary salt, gives, not the expected heptamethincyanine, but a pentamethincyanine. The mechanism of this reaction is discussed.

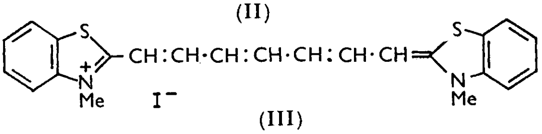
The pyridinium ring in certain pyridine quaternary salts can be readily ruptured with the formation of glutaconaldehyde or derivatives thereof; *e.g.*, Zincke, Heuser, and Möller[1] showed that the quaternary salt (I; R = 2,4-dinitrophenyl) gave glutaconaldehyde dianil hydrochloride (II) when treated with aniline. A recent comprehensive review[2] of these reactions deals also with the closely related reaction whereby a heptamethincyanine (tricarbocyanine), *e.g.*, (III), can be formed directly from some pyridine quaternary salts by reaction under alkaline conditions with a heterocyclic quaternary salt possessing a reactive methyl group. The quaternary salt (I; R = 2,4-dinitrophenyl) was originally used for this purpose,[3] and one of the present authors[4] described a similar reaction with a salt (I; R = 2-benzoxazolyl). In these reactions glutaconaldehyde was assumed to be a transient intermediate.

$$[\mathrm{Ph{\cdot}NH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}NHPh}]^{+}\mathrm{Cl}^{-}$$

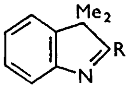
(II)



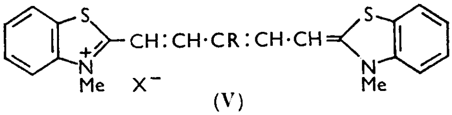
(I)



(III)



(IV)



(V)

We have prepared 2-chloro-3,3-dimethylindolenine (IV; R = Cl) by reaction of 3,3-dimethyloxindole with phosphorus pentachloride. This chloroindolenine has a very reactive halogen atom and reacts rapidly with water and with aniline to yield 3,3-dimethyloxindole and 2-anilino-3,3-dimethylindolenine (IV; R = NHPh) respectively. There is

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[1] Zincke, Heuser, and Möller, *Annalen*, 1904, **333**, 296.

[2] Creyf and Roosens, *Ind. chim. belge*, 1958, **23**, 855, 967; cf. Mosher, in Elderfield's " Heterocyclic Compounds," John Wiley and Sons, Inc., New York, 1950, Vol. I, p. 421.

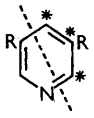
[3] Wahl and I.G. Farbenindustrie A.-G., G.P. 499,967/1928; Fisher and Hamer, *J.*, 1933, 189.

[4] Kendall, B.P. 424,264/1933.

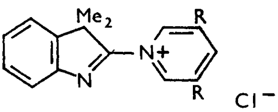
ready reaction when it is heated with 2,3-dimethylbenzothiazolium toluene-*p*-sulphonate in pyridine, but the product is the pentamethincyanine and not the expected heptamethincyanine (III). Isolated as its iodide, this product proved to be identical with the dye (V; R = H) prepared by treating 2,3-dimethylbenzothiazolium iodide with β-anilinoacraldehyde anil hydrochloride.[5]

This unexpected reaction involves the pyridine ring, since with 3,5-lutidine in place of pyridine the chain-substituted pentamethincyanine (V; R = Me) was obtained. This result indicated that the pyridine ring had split as shown in (VI), the carbon atoms marked * providing the three central atoms of the pentamethin chain. The fate of the remaining two carbon atoms is unknown. The reaction, involving cleavage of a carbon–carbon link under very mild conditions is apparently without parallel in the pyridine series, and the mechanism is by no means clear. Certainly it involves preliminary formation of pyridinium quaternary salts of type (VII), since these can be isolated; although these quaternary chlorides could not be obtained pure, a pure crystalline perchlorate was obtained on reaction of the salt (VII; R = H) with aqueous sodium perchlorate. Reaction with the benzothiazole quaternary salt in pyridine then leads to dyes (V; R = H and Me) from the quaternary salts (VII; R = H and Me respectively). However, with aniline in pyridine, the salt (VII; R = H) gives Zincke's salt (II) so that the pyridine ring has here split in the normal manner. Moreover, if the reaction of quaternary salt (VII; R = H) with the benzothiazole quaternary salt is carried out in ethanolic sodium ethoxide the chief product is the heptamethincyanine (III), the pentamethincyanine being a minor product; here also normal ring opening has occurred.

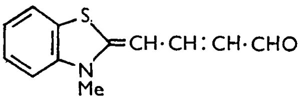
Clearly, the indoleninylpyridinium chloride (VII; R = H) can react with 2,3-dimethylbenzothiazolium toluene-*p*-sulphonate in two different ways: first, by a normal reaction leading to heptamethincyanine, and presumably involving an initial fission of the pyridine ring with the formation of glutaconaldehyde, under the action of a strong base (sodium ethoxide). In the more feebly basic pyridine, this ring opening to glutaconaldehyde does not occur, and the " abnormal " reaction supervenes; this presumably involves reaction of the benzothiazole quaternary salt (or the related methylene base) with the pyridinium salt before ring opening occurs. Normally, reaction at the 2-position of the pyridine ring might be expected to occur, leading eventually to a heptamethincyanine. In the case of the indoleninylpyridinium salts (VII), however, this evidently does not happen, owing possibly to steric hindrance by the *gem*-dimethyl group of the indolenine ring. Reaction of the benzothiazole salt at the 4-position of the pyridine residue in salt (VII) must be assumed to occur in this case, followed by fission of the pyridine ring as in (VI) to give an intermediate, possibly (VIII), which could react with a further molecule of benzothiazolium salt to give a pentamethincyanine.



(VI)



(VII)



(VIII)

The reaction of the chloroindolenine with 2,3-dimethylbenzothiazolium toluene-*p*-sulphonate in a number of other pyridine bases has been examined. Only with β-picoline was evidence for the formation of a dicarbocyanine obtained. With α- and γ-picoline, 2,6-lutidine, and 2,4,6-collidine no dicarbocyanine could be detected in the mixture of dyes formed, owing, presumably, to the presence of reactive methyl groups in these compounds. We have also attempted to extend the scope of the reaction by the use of other reactive halogen compounds in place of the chloroindolenine. Spectroscopic evidence

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[5] Piggott, Rodd, and I.C.I. Ltd., B.P. 355,693/1930.

for the formation of a pentamethincyanine was obtained in the reaction of 1-chloro-2,4-dinitrobenzene and of 2-chlorobenzothiazole with 2,3-dimethylbenzothiazolium toluene-*p*-sulphonate in pyridine: however, in both cases a mixture of dyes was formed and no pure material could be isolated.

EXPERIMENTAL

2-*Chloro*-3,3-*dimethylindolenine*.—A mixture of 3,3-dimethyloxindole [6] (50 g.) and phosphorus pentachloride (100 g., 1·5 mol.) was heated under reflux at 150—160° for 1 hr., by which time evolution of hydrogen chloride had practically ceased. As much volatile material as possible (mostly phosphoryl chloride) was then distilled off, the temperature of the bath being raised finally to 180°. The residue was then fractionated, to give fractions (i), b. p. 121—124°/22 mm. (36·7 g., 66%), and (ii) b. p. 140°/22 mm. to 160°/26 mm. (12·3 g.). Fraction (i) consisted of 2-*chloro*-3,3-*dimethylindolenine*, which was obtained as a fuming liquid, b. p. 114°/16 mm., n_D^{16} 1·5542 (Found: C, 66·3; H, 5·4. $C_{10}H_{10}NCl$ requires C, 66·8; H, 5·6%). The second fraction was a mixture, but was probably largely a 2,*x*-dichloro-3,3-dimethylindolenine. Use of equimolecular quantities of oxindole and phosphorus pentachloride led to incomplete reaction of the oxindole, whilst increase of the proportion of phosphorus pentachloride to 2 mols. increased the amount of high-boiling material at the expense of the chloroindolenine. The infrared spectrum of the chloroindolenine showed the following bands: 3070 and 2970 (CH stretch), 1720 (C=N stretch), 1590 (C=C stretch), 1550s, 1465 and 1450s (C=C stretch), 1380 and 1360 (CH deformation of *gem*-dimethyl group), 1330, 1305, 1260, 1210s, 1190, 1155, 1120, 1090, 1035s, 1015s, 990, 947, 869, 852, 827, 770s, 756s (CH out-of-plane deformation of *ortho*-disubstituted benzene), 687 cm.$^{-1}$.

Reactions of the Chloroindolenine.—When the chloroindolenine was warmed briefly with aqueous sodium carbonate a white solid was formed. After crystallisation from ethyl acetate, this had m. p. 149—150° alone or mixed with 3,3-dimethyloxindole (m. p. 151°).

The chloroindolenine (2·2 g.) was added to a solution of aniline (2·5 g.) in dry ether (20 ml.). After 2 hr. at room temperature, the ether was boiled off and the residue was washed with dilute hydrochloric acid and triturated with dilute aqueous sodium hydroxide solution. The product (2·71 g.) had m. p. 160—166°, and by successive crystallisations from aqueous ethanol and from cyclohexane, followed by sublimation under reduced pressure, yielded 2-*anilino*-3,3-*dimethylindolenine*, m. p. 169—170° (Found: C, 81·0; H, 6·7. $C_{16}H_{16}N_2$ requires C, 81·3; H, 6·8%).

A mixture of the chloroindolenine (3·5 g.) and dry pyridine (1·7 g.) was kept at room temperature for 16 hr. Addition of ether gave a solid which was washed successively with ether, acetone, and ethyl acetate to leave the quaternary chloride (VII; R = H) as a dark, deliquescent solid. A solution in a little hot water was treated with charcoal and filtered into an aqueous solution of sodium perchlorate. The precipitate was washed with a little cold water and crystallised from water, to yield 1-(3,3-*dimethyl*-2-*indoleninyl*)*pyridinium perchlorate* as pale yellow needles, m. p. 199—201° (Found: Cl, 11·15. $C_{15}H_{15}O_4N_2Cl$ requires Cl, 11·0%). Reaction of the chloroindolenine with 3,5-lutidine similarly gave the quaternary salt (VII; R = Me).

Reaction of the Chloroindolenine with Pyridine, etc., and 2,3-*Dimethylbenzothiazolium Toluene*-p-*sulphonate*.—(a) *Pyridine*. The chloroindolenine (0·90 g.) was added to a suspension of finely powdered 2,3-dimethylbenzothiazolium toluene-*p*-sulphonate (1·40 g.) in dry pyridine (10 ml.). After 10 days in a stoppered flask at room temperature, the mixture was added to a warm concentrated solution of potassium iodide in water. The precipitated dye was washed with boiling water, then with hot ethanol until the washings were pure blue (much brown material was removed). The residue was almost pure bis-(3-methyl-2-benzothiazole)pentamethincyanine iodide (0·70 g.), m. p. 286—288° (decomp.), and the cooled ethanol washings deposited a further crop (0·11 g.) of slightly less pure material (total yield 79%). The dye formed blue-green needles, m. p. 292—293° (decomp.) (Kendall [7] gives m. p. 281°), from 2-methoxyethanol (730 ml./g.) (Found: N, 6·0; S, 13·0; I, 25·6. Calc. for $C_{21}H_{19}N_2S_2I$: N, 5·7; S, 13·2; I, 25·9%), $\lambda_{max.}$ (in 2-methoxyethanol) 6525 Å (log ε 5·30) (Hamer and Rathbone [8] give $\lambda_{max.}$ 6500 in methanol). The dye was identical with that prepared in 40% yield by refluxing 2,3-dimethylbenzothiazolium iodide (1·46 g.) with β-anilinoacraldehyde anil hydrochloride (0·65 g.) in

[6] Brunner, *Monatsh.*, 1906, **27**, 1183.
[7] Kendall, B.P. 431,186/1933.
[8] Hamer and Rathbone, *J.*, 1945, 595.

ethanol (50 ml.) containing triethylamine (2·5 ml.) for 1 hr. The dyes had identical m. p.s and mixed m. p., although mixed m. p.s are unreliable in this series. However, the dyes proved to be identical also in their appearance, solubility, and light absorption, both in the visible and in the infrared region (2·5—15 μ). These criteria were also used in every other case to prove the identity of a pair of dyes.

(b) 3,5-*Lutidine*. The sample of base used was estimated by vapour-phase chromatography to have a 3,5-lutidine content of at least 99·5%. The dried (KOH) material distilled completely at 170—171°/765 mm. (Coulson and Ditcham[9] give b. p. 169—170°/767 mm.); the picrate had m. p. 238° and the methiodide, m. p. 274° (Oparina[10] gives m. p.s 238 and 275°, respectively). A mixture of 2,3-dimethylbenzothiazolium toluene-*p*-sulphonate (1·70 g.), 3,5-lutidine (2·0 ml.), and 2-chloro-3,3-dimethylindolenine (0·55 g.) was warmed on the steam-bath for 1½ hr., by which time much dye had crystallised. The mixture was boiled with methanol (20 ml.), and the dye (0·60 g., 44%) was filtered off after cooling. This proved to be *bis-(3-methyl-2-benzothiazole)-γ-methylpentamethincyanine toluene-*p*-sulphonate*, m. p. 239° (from methanol, 100 ml.), green needles (Found: C, 62·8; H, 5·6; N, 5·0; S, 16·7. $2C_{29}H_{28}O_3N_2S_3,CH_4O$ requires C, 62·7; H, 5·35; N, 5·0; S, 17·0%). A solution of the dye in warm 2-methoxyethanol was treated with aqueous potassium iodide solution to yield the *iodide*, blue-green needles, m. p. 283—284° (decomp.) (from 2-methoxyethanol, 175 ml./g.) (Found: C, 52·6; H, 4·7; N, 5·7; S, 12·8; I, 24·8. $C_{22}H_{21}N_2S_2I$ requires C, 52·4; H, 4·2; N, 5·6; S, 12·7; I, 25·2%), $\lambda_{max.}$ (in EtOH) 6510 Å (log ε 5·34). The dye was completely identical with that prepared as follows, by a modification of the method suggested by Ogata.[11] A mixture of 2-2′-ethylthiovinyl-3-methylbenzothiazolium iodide[12] (1·82 g.), methylmalonic acid (0·6 g.), and pyridine (30 ml.) was warmed on the steam-bath. After 1 hr. more methylmalonic acid (0·6 g.) was added and the mixture was refluxed for 1 hr. The crystals which separated on cooling were washed with ethanol to yield the dye (0·34 g.) which was obtained as blue-green needles (0·23 g.) from 2-methoxyethanol.

*Reaction of Quaternary Pyridinium Salts with 2,3-Dimethylbenzothiazolium Toluene-*p*-sulphonate.*—(a) *In pyridine.* A mixture of 1-(3,3-dimethyl-2-indoleninyl)-3,5-dimethylpyridinium chloride (VII; R = Me) (1·0 g.) and 2,3-dimethylbenzothiazolium toluene-*p*-sulphonate (2·3 g.) in pyridine (5·0 ml.) was warmed on the steam-bath for 1 hr. The resulting solution was diluted to 25 ml. with ethanol, then filtered, and the filtrate was treated with aqueous potassium iodide. The precipitated dye crystallised from 2-methoxyethanol to yield bis-(3-methyl-2-benzothiazole)-γ-methylpentamethincyanine iodide, m. p. 283—284° (decomp.), identical with that prepared as described above. On use of 1-(3,3-dimethyl-2-indoleninyl)-pyridinium chloride (VII; R = H), the product was bis-(3-methyl-2-benzothiazole)pentamethincyanine iodide.

(b) *In sodium ethoxide solution.* A cold solution of 1-(3,3-dimethyl-2-indoleninyl)pyridinium chloride (VII; R = H) (0·47 g.) and 2,3-dimethylbenzothiazolium toluene-*p*-sulphonate (1·22 g.) in ethanol (15 ml.) was treated with cold sodium ethoxide solution (2 g. of sodium per 100 ml.; 4 ml.). After 30 min. a concentrated solution of potassium iodide (10 g.) in water was added, and the precipitated solid was washed with boiling water and crystallised from methanol (650 ml./g.) to yield dark green *bis-(3-methyl-2-benzothiazole)heptamethincyanine iodide* (0·23 g.), m. p. 216—217° (decomp.) (Found: C, 53·5; H, 4·5; S, 12·4. $C_{23}H_{21}N_2S_2I$ requires C, 53·5; H, 4·1; S, 12·5%), $\lambda_{max.}$ (in MeOH) 7520 Å (log ε 5·38). Evaporation of the mother-liquors from the recrystallisation to small volume yielded a solid (0·01 g.) which appeared spectroscopically to be largely pentamethincyanine. The heptamethincyanine was identical with the dye prepared by reaction of 1-2′-benzoxazolylpyridinium chloride with 2,3-dimethylbenzothiazolium toluene-*p*-sulphonate by Kendall's method.[4]

Reaction of Quaternary Salt (VII; R = H) *with Aniline.*—A mixture of the chloroindolenine (1·1 g.) and pyridine (5·0 ml.) was kept at room temperature for 3 hr. Addition of aniline (2·0 ml.) caused the solution to become deep red, and red crystals soon separated. After 30 min. these were filtered off and washed with a little ethanol, giving glutaconaldehyde dianil hydrochloride (1·09 g.) as red needles with a blue reflex, m. p. 153—154° undepressed on admixture with an authentic specimen.[1]

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[9] Coulson and Ditcham, *J.*, 1957, 356.

[10] Oparina, *J. Russ. Phys. Chem. Soc.*, 1929, **61**, 2001; *Chem. Abs.*, 1930, **24**, 3790.

[11] Ogata, *Bull. Inst. Phys. Chem. Res. Japan*, 1937, **16**, 631.

[12] Kendall and Majer, *J.*, 1948, 687.

The visible spectra were measured on a Unicam SP. 500 spectrophotometer, and the infrared spectra on an Infracord spectrophotometer, model 137.

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