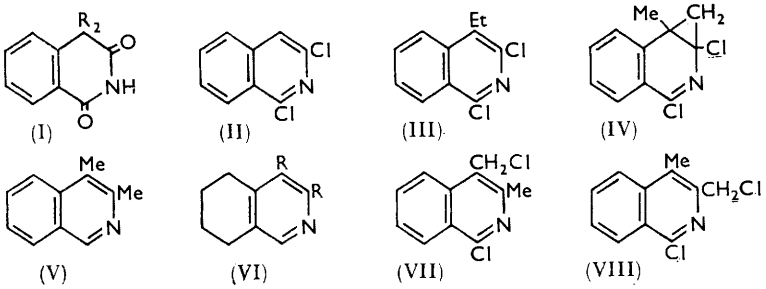
378. *The Rearrangement of αα-Dimethylhomophthalimide (1,2,3,4-Tetrahydro-4,4-dimethyl-1,3-dioxoisoquinoline) to a Derivative of 3,4-Dimethylisoquinoline.*

By GURNOS JONES.

Treatment of αα-dimethylhomophthalimide with phosphorus oxychloride at 200° gives a 1-chloro-3-chloromethyl-4-methylisoquinoline. The mechanism of the rearrangement is discussed.

ONE of the earliest syntheses of isoquinoline was that due to Gabriel,[1] who converted homophthalimide (1,2,3,4-tetrahydro-1,3-dioxoisoquinoline) (I; R = H) into 1,3-dichloroisoquinoline (II) by treatment with phosphorus oxychloride, and reduced this to isoquinoline by hydriodic acid and red phosphorus. He subsequently reported [2] a similar sequence of reactions starting from αα-dimethylhomophthalimide (I; R = Me), in which he obtained a dichloro-compound, $C_{11}H_9NCl_2$, and reduced this to a homologue of isoquinoline, $C_{11}H_{11}N$. Gabriel suggested formula (III) or (IV) for the dichloro-compound.

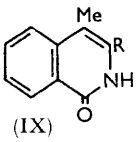


If formula (III) is correct the $C_{11}H_{11}N$ base must be 4-ethylisoquinoline (under which formula it is reported in the literature [3]); if formula (IV) is correct the base might be 3,4-dimethylisoquinoline, a cyclopropyl structure appearing to be unlikely. Synthesis of 4-ethylisoquinoline [4] and comparison of the pure base and of its picrate with Gabriel's $C_{11}H_{11}N$ base and its picrate showed them to be different. Comparison of the latter base with synthetic 3,4-dimethylisoquinoline (V), however, showed them to be identical. Hence, rearrangement has taken place and the dichloro-compound seemed likely to be a derivative of 3,4-dimethylisoquinoline.

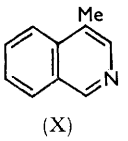
The infrared absorption of the dichloro-compound showed bands at 1600, 1560, and 1550 cm.$^{-1}$ (C=C and C=N vibrations [5]) and at 770 cm.$^{-1}$ (CH out-of-plane deformation characteristic of an isoquinoline unsubstituted in the carbocyclic ring). Thus the dichloro-compound is an isoquinoline having both chlorine atoms bound directly or through a substituent to the heterocyclic ring. The ultraviolet absorption of the dichloro-compound resembled those of 1-chloroisoquinoline and of 1,3-dichloroisoquinoline (see Figure); in its feebly basic nature the dichloro-compound also resembled 1-chloroisoquinolines and these observations together with its mode of formation led to the formulation of the dichloro-compound as a derivative of 1-chloroisoquinoline. Catalytic reduction of the dichloro-compound at atmospheric temperature and pressure led to the absorption of four mols. of hydrogen and gave a chlorine-free base, $C_{11}H_{15}N$, whose ultraviolet absorption

[1] Gabriel, *Ber.*, 1886, **19**, (*a*) 1653, (*b*) 2354.
[2] Gabriel, *Ber.*, 1887, **20**, 1205.
[3] Heilbron and Bunbury, " Dictionary of Organic Compounds," Eyre and Spottiswoode, revised edn., 1953, p. 513.
[4] Jones, *J.*, in the press.
[5] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 234.

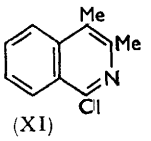
closely resembled that of 2,3,4,5-tetramethylpyridine,[6] and a similar reduction of 1,3-dichloroisoquinoline gave 5,6,7,8-tetrahydroisoquinoline (VI; R = H); hence the formula (VI; R = Me) appears the most probable for the reduced base. The methiodide of the base (VI; R = Me) showed the expected bathochromic shift of the ultraviolet absorption maximum. The formation of such a reduced chlorine-free base with the uptake of only four mols. of hydrogen excludes Gabriel's formula (IV) for the dichloro-compound. The most likely structures for the dichloro-compound appeared to be (VII) or (VIII); in both of these, the benzylic chlorine atoms should be easily removed by reduction. A degradative sequence was devised (shown by VIII ⟶ X) which established (VIII) as the correct structure for Gabriel's dichloro-compound.



(IX)

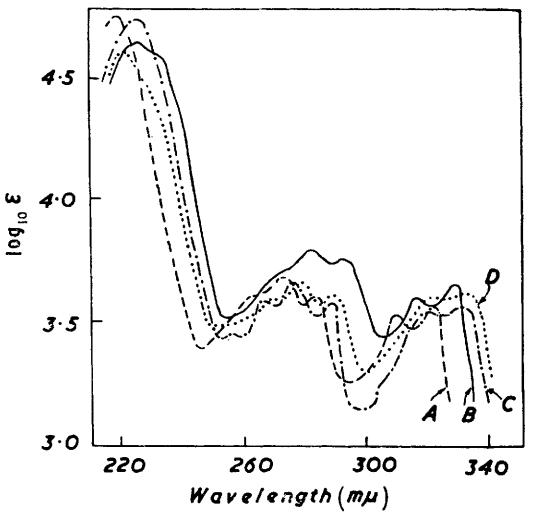


(X)



(XI)

(*A*) – – – – 1-Chloroisoquinoline.
(*B*) —— Dichloro-compound (VIII).
(*C*) — · — · — 1,3-Dichloroisoquinoline.
(*D*) . . . . Monochloro-compound (XI).

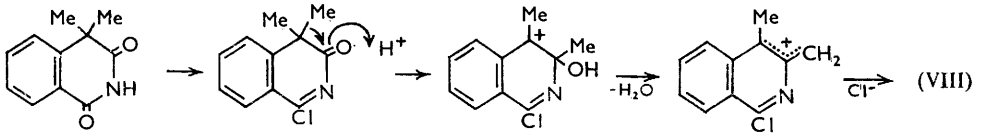


The first attempts to convert the dichloro-compound (VIII) into the hydroxymethyl derivative by hydrolysis with aqueous-ethanolic sodium hydroxide were unsuccessful; a liquid was obtained, and its infrared absorption showed a strong band at 1110 cm.$^{-1}$ (C–O stretching in ethers). Gabriel has reported[15] the equally ready conversion of 1,3-dichloroisoquinoline into 3-chloro-1-ethoxyisoquinoline. Treatment of the dichloro-compound (VIII) in hot acetic acid with silver acetate gave an isocarbostyril derivative (IX; R = CH_2·OAc); presumably the initial replacement of both chlorine atoms by acetate ions is followed by hydrolysis (during the working up) of the unstable *O*-acetylisocarbostyril so formed (2-acetoxypyridine is hydrolysed in cold water [7]). The isocarbostyril derivative, which was difficult to crystallise and failed to give a good analysis, showed infrared absorption bands at 1740 cm.$^{-1}$ (ester C=O) and at 1645 cm.$^{-1}$ (lactam C=O); it was readily hydrolysed to the alcohol (IX; R = CH_2·OH). This alcohol had an infrared absorption in which the strong band at 1740 cm.$^{-1}$ shown by the acetate was absent, but which showed the band at 1645 cm.$^{-1}$ (lactam C=O) and a new band at 1010 cm.$^{-1}$ (CO stretching in a benzylic alcohol). Furukawa has reported [8] that hydroxymethyl-pyridines and -quinolines can be oxidised to the corresponding carboxylic acid by potassium permanganate in acetone.

[6] Ikekawa, Maruyama, and Sato, *Pharm. Bull.* (*Japan*), 1954, **2**, 209.
[7] Chichibabin and Szakow, *Ber.*, 1935, **58**, 2600.
[8] Furukawa, *Pharm. Bull.* (*Japan*), 1955, **3**, 413.

The alcohol (IX; R = CH_2·OH) was sparingly soluble in acetone but was oxidised as a suspension in warm acetone by the theoretical quantity of potassium permanganate, giving the known [9] 4-methylisocarbostyril-3-carboxylic acid (IX; R = CO_2H). Decarboxylation of this acid gave 4-methylisocarbostyril (IX; R = H); both these compounds (IX; R = CO_2H or H) agreed in m. p. and ultraviolet absorption with those reported.[9] Distillation of the isocarbostyril (IX; R = Me) from zinc dust gave 4-methylisoquinoline (X), isolated as its picrate which did not depress the m. p. of synthetic 4-methylisoquinoline picrate. Hence the structure (VIII) must represent the dichloro-compound.

Gabriel reported [2] that reduction of the dichloro-compound (VIII) with hydriodic acid and red phosphorus at a lower temperature than that required to produce the $C_{11}H_{11}N$ base gave a small yield of a monochloro-compound, $C_{11}H_{10}NCl$. This has been isolated: its ultraviolet absorption resembles that of the dichloro-compound (VIII) and other 1-chloroisoquinolines (see Figure). Hence this monochloro-compound is probably 1-chloro-3,4-dimethylisoquinoline (XI).



Little evidence is available for the mechanism of the rearrangement. It was found that the yield of dichloro-compound was highest when old specimens of phosphorus oxychloride were used, lowest with fresh specimens, indicating the probable necessity for some free acid. This suggests a protonation at some stage and, as the first stage of the rearrangement seems likely to be the replacement of the oxygen in the 1-position by chlorine, the annexed mechanism is suggested.

Since the reaction mentioned above between the dichloro-compound (VIII) and silver acetate appeared to offer a convenient general method for the conversion of a 1-chloroisoquinoline into the corresponding isocarbostyril, the interaction of 1-chloroisoquinoline itself with silver acetate was examined. Isocarbostyril was obtained in 60% yield, and there seems no doubt that such replacements could be achieved also with 2- or 4-chloroquinolines, and with 2- or 4-chloropyridines.

Experimental

M. p.s were determined on a Kofler block unless otherwise stated.

Homophthalimide.—This was prepared by Bailey and Swallow's method.[10] Methylation by Gabriel's method [11] gave the dimethyl derivative, best purified by recrystallisation from cyclohexane.

Reaction with Phosphorus Oxychloride.—This was effected as described by Gabriel; [2] 8 g. of αα-dimethylhomophthalimide (1,2,3,4-tetrahydro-4,4-dimethyl-1,3-dioxoisoquinoline) gave 5 g. (53%) of dichloro-compound, m. p. 166°, after one recrystallisation from ethanol; it had $\lambda_{max.}$ 2245, 2810, 2920, 3170, 3290 Å ($\log_{10}$ ε 4·64, 3·79, 3·76, 3·60, 3·66) in 95% EtOH (see Figure).

Reduction of Dichloro-compound with Hydriodic Acid and Red Phosphorus.—The base obtained by Gabriel's method [3] gave a picrate, m. p. 212—213°, undepressed by a synthetic specimen [11] of 3,4-dimethylisoquinoline picrate, m. p. 213°. The pure base, regenerated from pure picrate and distilled, had $\lambda_{max.}$ 2735, 3025, 3140, 3230, 3285 Å ($\log_{10}$ ε 3·65, 3·25, 3·53, 3·53, 3·67) in hexane. 3,4-Dimethylisoquinoline had $\lambda_{max.}$ 2735, 3025, 3140, 3230, 3285 Å ($\log_{10}$ ε 3·68, 3·30, 3·54, 3·53, 3·68) in hexane. The infrared absorption of the two bases was identical.

5,6,7,8-*Tetrahydro*-3,4-*dimethylisoquinoline.*—The dichloro-compound (VIII) (0·2 g.) in glacial acetic acid (25 ml.) was hydrogenated at 27·5°/745 mm. with Adams catalyst (30 mg.)

[9] Dijksman and Newbold, *J.*, 1951, 1213.
[10] Bailey and Swallow, *J.*, 1956, 2477.
[11] Gabriel, *Ber.*, 1887, **20**, 1198.

(hydrogen uptake, 79·3 ml. at N.T.P. Calc. for 4 mols., 80 ml.). The acetic acid was removed under reduced pressure, and the residue basified and extracted with chloroform. The chloroform solution was dried (Na_2SO_4) and evaporated, and the residue divided in two parts. (*a*) The first part was treated with ethanolic picric acid, giving the *picrate*, m. p. 211—212° (from ethanol) (Found: C, 52·3; H, 4·7; N, 14·3. $C_{17}H_{18}N_4O_7$ requires C, 52·3; H, 4·65; N, 14·35%); the base regenerated from the pure picrate and distilled had $\lambda_{max.}$ 2680 Å ($\log_{10}\varepsilon$ 3·55) in 95% EtOH. (*b*) The second part was dissolved in acetone and treated with methyl iodide, giving the *methiodide*, forming colourless prisms, m. p. 147°, from ethyl acetate–ethanol (Found: C, 47·8; H, 5·7. $C_{12}H_{18}NI$ requires C, 47·5; H, 6·0%), $\lambda_{max.}$ 2770 Å ($\log_{10}\varepsilon$ 3·79) in 95% EtOH.

5,6,7,8-*Tetrahydroisoquinoline*.—Similar reduction of 1,3-dichloroisoquinoline gave the tetrahydroisoquinoline picrate, m. p. 144—145° (lit.,[12] m. p. 144°) (Found: C, 50·0; H, 3·8. Calc. for $C_{15}H_{14}N_4O_7$: C, 49·7; H, 3·9%).

3-*Hydroxymethyl*-4-*methylisocarbostyril* (IX; R = CH_2·OH).—(*a*) The dichloro-compound (VIII) (1 g.) in acetic acid (50 ml.) was heated and stirred on the water-bath for 3 hr. with silver acetate (3 g.). The hot mixture was filtered, then cooled and re-filtered, the filtrate evaporated under reduced pressure, and the residue treated with aqueous ammonia (*d* 0·88) and chloroform. The chloroform extract was dried (Na_2SO_4) and evaporated, and the residue crystallised from ethyl acetate to give the acetate (IX); R = CH_2·OAc as needles, m. p. 210—215° (indistinct, even after repeated recrystallisation). In subsequent experiments the residue from the chloroform extract was not crystallised, but washed with cold ethyl acetate and then hydrolysed. (*b*) The purified acetate (0·4 g.) was dissolved in ethyl alcohol–water (1 : 1; 50 ml.) with sodium hydroxide (5 g.) and heated under reflux for 1 hr. The alcohol was evaporated off, the solution cooled and acidified (to assist filtration), and the solid *hydroxymethyl compound* filtered off. Recrystallisation from methanol gave prisms (0·2 g.), m. p. 218° (Found: C, 69·8; H, 5·8; N, 7·6. $C_{11}H_{11}O_2N$ requires C, 69·8; H, 5·9; N, 7·4%), $\lambda_{max.}$ 2310, 2850, 3320 Å ($\log_{10}\varepsilon$ 4·16, 3·95, 3·67) in 95% EtOH. When the intermediate acetate was not purified, 5 g. of dichloro-compound gave 2·6 g. of hydroxymethyl compound, m. p. 216—218° (62%).

Isocarbostyril from 1-*Chloroisoquinoline*.—Preparation, as described above, from 1-chloroisoquinoline (3 g.) and silver acetate (5 g.) in acetic acid (100 ml.) gave a yield of once-recrystallised isocarbostyril, m. p. 205—206°, of 1·6 g. (60%).

4-*Methylisocarbostyril*-3-*carboxylic Acid* (IX; R = CO_2H).—The hydroxymethyl compound (0·98 g.) was suspended in warm acetone (100 ml.) and powdered potassium permanganate (0·6 g.) was added in portions, with shaking. After being stored for 1 hr., the mixture was filtered, and the manganese dioxide was thoroughly extracted with hot water. The combined filtrates were evaporated under reduced pressure, and the residue was extracted with hot water and filtered. The filtrate was acidified with acetic acid, and the solid acid was collected. Recrystallised from methanol, the acid had m. p. 335—336° (rapid heating in a sealed capillary) (0·3 g., 28·5%) (Found: C, 64·6; H, 4·7. Calc. for $C_{11}H_9O_3N$: C, 65·0; H, 4·5%), $\lambda_{max.}$ 2110, 2270, 2500,* 3060, 3240 * Å ($\log_{10}\varepsilon$ 4·45, 4·22, 3·86, 4·08, 3·96) in 95% EtOH. Dijksman and Newbold report [9] for 4-methylisocarbostyril-3-carboxylic acid, m. p. 335—336°, $\lambda_{max.}$ 2120, 2270, 2540, 3070, 3250 * Å ($\log_{10}\varepsilon$ 4·32, 4·16, 3·77, 4·09, 3·92) in EtOH.

4-*Methylisocarbostyril* (IX; R = H).—The acid (IX; R = CO_2H) was decarboxylated as described by Dijksman and Newbold,[9] giving 4-methylisocarbostyril, m. p. 172—173° (lit.,[9] m. p. 172—173°), $\lambda_{max.}$ 2270, 2850, 3300 Å ($\log_{10}\varepsilon$ 4·18, 3·92, 3·71) in EtOH [lit.,[9] $\lambda_{max.}$ 2250, 2850, 3310 Å ($\log_{10}\varepsilon$ 4·20, 3·94, 3·73) in EtOH].

4-*Methylisoquinoline* (X).—The isocarbostyril (IX; R = H) was heated to dull red heat in a Pyrex bulb tube with ten times its weight of zinc dust. The distillate was treated with ethanolic picric acid, giving 4-methylisoquinoline picrate, m. p. 202—203°: (from EtOH), undepressed when mixed with synthetic 4-methylisoquinoline picrate. The base was regenerated from the purified picrate by treatment with lithium hydroxide and distilled; it had $\lambda_{max.}$ 2710, 2960, 3020, 3080, 3150, 3215 Å ($\log_{10}\varepsilon$ 3·64, 3·19, 3·24, 3·43, 3·38, 3·62) in hexane. Synthetic 4-methylisoquinoline had $\lambda_{max.}$ 2710, 2960, 3030,* 3080, 3150, 3215 Å ($\log_{10}\varepsilon$ 3·67 3·22, 3·27, 3·43, 3·44, 3·53) in hexane.

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* Inflection.

[12] Witkop, *J. Amer. Chem. Soc.*, 1948, **70**, 1424.