181. *The Mechanism of Heterocyclic Ring Expansions. Part I. The Reaction of 2,3-Dimethylindole with Dichlorocarbene.*

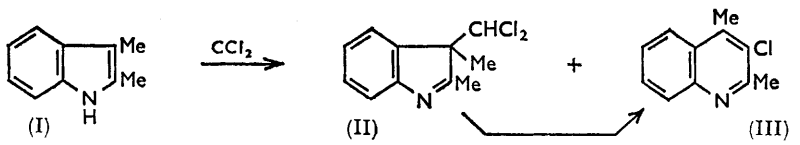
By C. W. Rees and C. E. Smithen.

2,3-Dimethylindole is converted into 3-dichloromethyl-2,3-dimethyl-3*H*-indole (II) and 3-chloro-2,4-dimethylquinoline (III) by chloroform and sodium ethoxide, but the 3*H*-indole (II) is not an intermediate in the formation of the quinoline (III), as has been claimed. The 3*H*-indole is not convertible into the quinoline but is slowly hydrolysed to 2-acetamido-β-chloro-α-methylstyrene (XI) which is isomerised by acid to 4-chloromethyl-2,4-dimethyl-4*H*-3,1-benzoxazine (XVI) and not cyclised to the quinoline (III); thus a previously suggested route to the quinoline can be discounted.

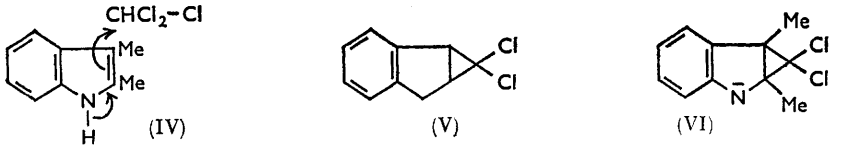
2,3-Dimethylindole yields the same two products, (II) and (III), with dichlorocarbene generated in other ways. Our results suggest that the quinoline is formed by ring-expansion of the labile indole–carbene adduct (VII), and the 3*H*-indole by reaction of dichlorocarbene with the ambidentate indolyl anion (IX).

The idea that dichlorocarbene is an intermediate in the basic hydrolysis of chloroform was suggested one hundred years ago by Geuther.[1] At the end of the last century Nef [2] used this concept to explain several other reactions involving chloroform and a base, including the ring-expansion of pyrroles to pyridines [3] and of indoles to quinolines.[4] The first convincing evidence for the formation of dichlorocarbene came from the kinetics of the basic hydrolysis of chloroform, which were consistent with rate-determining loss of a chloride ion from the trichloromethyl anion formed in a pre-equilibrium step; the dichlorocarbene so formed was rapidly hydrolysed.[5] Much evidence for this and other carbenes as reaction intermediates, especially their trapping with olefins to give cyclopropanes,[6] has since accumulated and has been reviewed.[7]

The expansion of five- to six-membered heterocyclic rings under strongly basic conditions, such as the conversion of pyrrole into pyridine, 3-bromopyridine, and 3-phenylpyridine with di-iodomethane, bromoform, and benzylidene chloride, respectively,[8] and of



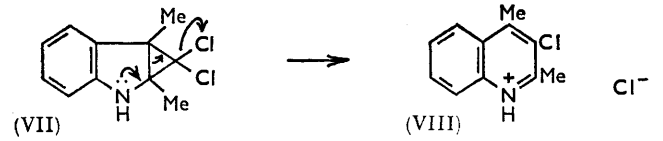
indole into 3-chloroquinoline with chloroform,[9] all proceed under conditions favourable to the formation of carbenes; although these reactions have limited synthetic value, their mechanisms are thus of considerable interest.



[1] Geuther, *Annalen*, 1862, **123**, 121.
[2] Nef, *Annalen*, 1897, **298**, 366.
[3] Ciamician and Dennstedt, *Ber.*, 1881, **14**, 1153; 1882, **15**, 1172.
[4] Magnanini, *Ber.*, 1887, **20**, 2608; 1888, **21**, 1940.
[5] Hine, *J. Amer. Chem. Soc.*, 1950, **72**, 2438.
[6] Doering and Hoffmann, *J. Amer. Chem. Soc.*, 1954, **76**, 6162.
[7] Kirmse, *Angew. Chem.*, 1959, **72**, 537; 1961, **74**, 161; Hine, "Physical Organic Chemistry," 2nd edn., McGraw-Hill, New York, 1962; Miginiac, *Bull. Soc. chim. France*, 1962, 2000; Chinoporos, *Chem. Rev.*, 1963, **63**, 235.
[8] Ciamician, *Ber.*, 1904, **37**, 4201, and references therein.
[9] Ellinger, *Ber.*, 1906, **39**, 2515.

A variant of the Reimer–Tiemann reaction,[10] using chloroform or bromoform and ethanolic sodium ethoxide, was applied by Plancher and Carrasco [11] to several pyrroles and indoles. Of particular mechanistic interest was their isolation of certain dichloromethyl-3*H*-pyrroles and -3*H*-indoles (dichloromethyl-indolenines and -pyrrolenines) in addition to the monochloro-products of ring-expansion, and their demonstration that the former were convertible into the latter. 2,3-Dimethylindole (I), for example, gave 3-dichloromethyl-2,3-dimethyl-3*H*-indole (II) and 3-chloro-2,4-dimethylquinoline (III), and the 3*H*-indole (II) was converted into the quinoline (III) on further treatment with hot ethanolic sodium ethoxide.[11] They considered the chloroform to act as a simple alkyl halide in alkylating the indole 3-position (as IV), and the 3*H*-indole structure rested on this analogy; they concluded that the 3*H*-indole was an intermediate in the ring-expansion.

Interest in this reaction, in which dichlorocarbene is presumably involved, was revived by the demonstration of a similar ring-expansion of indene to 2-chloronaphthalene by way of the carbene adduct (V).[12] Nakazaki [13] proposed addition of dichlorocarbene to the indolyl anion to give the 2,3-adduct (VI) as the common precursor for both the 3*H*-indole (II) and the quinoline (III), though the preference of the carbene for the double bond rather than the nucleophilic centres of the ambidentate indolyl anion was not explained. However, in the absence of good evidence for the structure of the 3*H*-indole (II) and of a reasonable mechanistic justification for its conversion into the quinoline (III), it was obviously tempting to consider that Plancher's indolenine (3*H*-indole) (II) was actually the isomeric dichlorocarbene adduct (VII). Then, at least, ring-expansion [(VII) ⟶ (VIII)] would be reasonable, being analogous to the conversion of the indene adduct (V) into 2-chloronaphthalene. This possibility has now been investigated.



(VII) (VIII)

Experimental

Boiling points and melting points are corrected. Infrared spectra were determined, for Nujol mulls (solids) or capillary films (liquids), using a Grubb-Parsons double-beam spectrophotometer with sodium chloride optics. Ultraviolet spectra were determined for absolute ethanol solutions with a Unicam S.P. 500 spectrophotometer; log ε is given in parentheses after λ. Gas–liquid chromatograms were obtained on a Pye "Argon" chromatograph. Active alumina refers to Spence Type H, deactivated alumina to Spence Type H shaken with 5% (w/w) of 10% aqueous acetic acid until homogeneous, and neutral alumina to Woelm, activity grade 1. Light petroleum refers to the fraction of b. p. 60—80° unless stated otherwise; organic extracts were dried with anhydrous magnesium sulphate, and evaporated by distillation in a rotary evaporator. Reaction products were identified wherever possible by mixed m. p. and by infrared comparison.

Materials.—2,3-Dimethylindole, prepared by Kissman, Farnsworth, and Witkop's method,[14] had b. p. 136—138°/5 mm. and solidified to a pale yellow crystalline mass, m. p. 98—99°; it was stored in this form in the dark under nitrogen. Crystallisation from ether–light petroleum gave almost colourless plates, m. p. 102—103° (lit.,[14] 100—102°). Chloroform used for generating dichlorocarbene was AnalaR grade, not further purified. Ethyl trichloroacetate (L. Light & Co.) was distilled, and the fraction of b. p. 55—56°/12 mm., n_D^{25} 1·4480 (lit.,[15] b. p. 50·5—51·5°/8 mm., n_D^{25} 1·4477), was used. Sodium trichloroacetate was prepared by neutralisation of an ice-cold solution of trichloroacetic acid (AnalaR grade, B.D.H. Ltd.) in absolute

[10] Wynberg, *Chem. Rev.*, 1960, **60**, 169.
[11] Plancher and Carrasco, *Atti Accad. naz. Lincei*, (*a*) 1904, **13**, I, 574; 1905, **14**, I, 162; (*b*) 1905, **14**, I, 705.
[12] Parham, Reiff, and Swartzentruber, *J. Amer. Chem. Soc.*, 1956, **78**, 1437.
[13] Nakazaki, *J. Chem. Soc. Japan*, 1955, **76**, 1169.
[14] Kissman, Farnsworth, and Witkop, *J. Amer. Chem. Soc.*, 1952, **74**, 3948.
[15] Parham and Schweizer, *J. Org. Chem.*, 1959, **24**, 1733.

methanol with a solution of sodium methoxide in methanol, under anhydrous conditions. Excess of methanol was removed at room temperature under reduced pressure and the resulting white crystalline solid was dried over phosphoric oxide. Immediately before use the salt was dried over phosphoric oxide at 100°/12 mm. Potassium t-butoxide was prepared by dissolving potassium in dry t-butyl alcohol heated under reflux, followed by distillation. The residue was powdered, and dried over phosphoric oxide at 120°/12 mm. for 3 hr. This product consumed 1·06 ± 0·01 equiv. (4 determinations) of 0·1N-hydrochloric acid (Bromothymol Blue). Potassium t-butoxide which had been dried by azeotropic distillation with heptane [16] or by heating at 50° in a high vacuum [17] was reported to consist of a 1 : 1-complex of potassium t-butoxide and t-butyl alcohol (which would have consumed only 0·6 equiv. of acid). Sodium methoxide was prepared and dried before use in the same way. Olefin-free light petroleum was obtained by shaking light petroleum (b. p. 40—60°) (500 ml.) thoroughly with sulphuric acid (5 × 100 ml.) and then with water, and was dried over sodium hydroxide; it then gave negligible positive reaction for unsaturation. 1,2-Dimethoxyethane was boiled under reflux with potassium for 3 hr. and then fractionally distilled from fresh potassium through a short helices-packed column and collected under nitrogen; the fraction of b. p. 87°, stored in the dark under nitrogen, was chromatographically (vapour phase) homogeneous.

Reaction of 2,3-Dimethylindole with Dichlorocarbene.—(a) *Under Plancher–Carrasco conditions.* The treatment of dimethylindole with chloroform and sodium ethoxide and isolation of the products by fractional crystallisation of their picrates from ethanol, as described by Plancher and Carrasco,[11a] gave yellow needles of 3-chloro-2,4-dimethylquinoline picrate, m. p. 212°, and orange prisms of 3-dichloromethyl-2,3-dimethyl-3*H*-indole picrate, m. p. 163°, as they described. A better procedure was as follows. 2,3-Dimethylindole (10 g.) was dissolved in absolute ethanol (50 ml.) containing sodium ethoxide (from sodium, 1·5 g.). Chloroform (1 g.) was added and the stirred reaction mixture was heated in a water-bath to 50—55° at which temperature first indications of reaction were observed. More chloroform (9 g.) was added dropwise during 2 hr. while the temperature was maintained at 50—55°; the mixture was stirred at this temperature overnight. Volatile materials were removed at 50°/15 mm., and the oily residue was dissolved in ether (150 ml.) and extracted with ice-cold 10% hydrochloric acid (5 × 50 ml.). The ethereal solution was washed with water, dried, and evaporated to give the crude non-basic fraction (10 g.) which solidified on cooling. The acidic extracts were made alkaline with 10N-aqueous potassium hydroxide, keeping the temperature below 10°, and the basic products extracted with ether (5 × 80 ml.). The ethereal solution was dried and evaporated, finally at 45°/15 mm., to give the crude basic fraction (3·8 g.) which crystallised on standing. This fraction was adsorbed on deactivated alumina (2 × 38 cm.) and eluted as follows. (*i*) Light petroleum (1 l.) then ether (5%) in light petroleum (500 ml.) gave an oil (1·45 g.) which on cooling yielded a solid, m. p. 71°, which gave 3-chloro-2,4-dimethylquinoline, m. p. 73° (from hexane) (lit.,[11a] 75°). This base showed typical quinoline absorption [$\lambda_{max.}$ 278 (3·63), 293sh (3·57), 307 (3·55), 321 (3·62); $\lambda_{min.}$ 248 (3·35), 304 (3·42), and 316 (3·35) mμ], and was dechlorinated to 2,4-dimethylquinoline (see below). Its *methotoluene-p-sulphonate* crystallised from benzene–methanol as needles, m. p. 200° (Found: C, 60·0; H, 5·1. $C_{19}H_{20}ClNO_3S$ requires C, 60·4; H, 5·3%); the *methiodide*, best prepared from the methotoluene-*p*-sulphonate with sodium iodide in methanol, crystallised from benzene–methanol as yellow plates, m. p. 230° (decomp.) (Found: C, 43·5; H, 4·0. $C_{12}H_{13}ClIN$ requires C, 43·2; H, 3·8%); the *methopicrate*, prepared from the methotoluene-*p*-sulphonate with lithium picrate in methanol, crystallised from ethanol as needles, m. p. 197—198° (decomp.) (Found: C, 49·2; H, 3·5. $C_{18}H_{15}ClN_4O_7$ requires C, 49·7; H, 3·5%). (*ii*) Ether (10%) in light petroleum (1 l.) then ether (20%) in light petroleum (500 ml.) gave a yellow oil (1·17 g.) which on cooling gave prisms, m. p. 72—74°, which yielded 3-dichloromethyl-2,3-dimethyl-3*H*-indole as very pale yellow prisms, m. p. 76—77° (from hexane) (lit.,[11a] 73—74°). This base showed typical 3*H*-indole absorption [$\lambda_{max.}$ 262 (3·71); $\lambda_{min.}$ 235 (3·33) mμ; $\nu_{max.}$ 1618w, 1587 (aryl–N=C), 767 ($CHCl_2$), 752 and 746 $cm.^{-1}$ (*o*-disubstituted benzene)], and gave a picrate, m. p. 166—167°, a methiodide, m. p. 213—214° (decomp.), and a methopicrate, m. p. 148—149° (decomp.) [lit.[11a,b] m. p.'s 164—165°, 220—221° (decomp.), and 146—147°, respectively].

The non-basic fraction (10 g.) of the reaction product was adsorbed on deactivated alumina

[16] Speziale and Ratts, *J. Amer. Chem. Soc.*, 1962, **84**, 854.
[17] Milas and Djokic, *Chem. and Ind.*, 1962, 405.

(3·5 × 30 cm.) and eluted as follows. (*i*) Light petroleum (1·5 l.) gave a crystalline solid (5·4 g.), m. p. 96—98°, identical (mixed m. p. and infrared) with 2,3-dimethylindole. (*ii*) Ether (5%) in light petroleum (500 ml.) then ether (10%) in light petroleum (500 ml.) gave a pale yellow oily solid (0·52 g.), m. p. 54—64°, largely 3-dichloromethyl-2,3-dimethyl-3*H*-indole not removed by the original acid extraction; it formed a picrate (0·9 g.), red prisms, m. p. 163° (from ethanol) undepressed on admixture with the authentic picrate of m. p. 166—167°. Examination of the infrared spectrum suggested that the second component of the mixture was 2-acetamidoacetophenone. In subsequent experiments this mixture was separated by further chromatography on deactivated alumina (1 × 20 cm.), and the 3*H*-indole was eluted quantitatively with ether (10%) in light petroleum. (*iii*) Ether (20%) in light petroleum (200 ml.) gave yellow needles (0·67 g.), m. p. 66—69°, which yielded almost colourless needles of 2-acetamidoacetophenone, m. p. 76—77° (from pentane) (lit.,[18] 77°) (Found: C, 67·6; H, 6·3. Calc. for $C_{10}H_{11}NO_2$: C, 67·8; H, 6·3%), $\lambda_{max.}$ 228—234 (4·45), 258 (4·06), 266 (3·99), and 324 (3·66), $\lambda_{min.}$ 244 (3·85), 263 (3·95), and 280 (2·98) mμ, in accord with that reported by Grammaticakis,[18] $\nu_{max.}$ 3225 (bonded N–H), 1690 (aryl ketone C=O), 1655 (sec. amide C=O), 1610 (aromatic C=C), and 1585 cm.$^{-1}$ (conj. aromatic C=C.) The compound gave an iodoform test, a reaction with 2,4-dinitrophenylhydrazine, and an oxime, m. p. 149° (lit.,[19] 153°) *acetyl derivative*, m. p. 133° (Found: C, 61·3; H, 6·2. $C_{12}H_{14}N_2O_3$ requires C, 61·5; H, 6·0%). (*iv*) Ether (50%) in light petroleum (200 ml.) gave yellow prisms (0·10 g.), m. p. 170—175° (decomp.), which after repeated recrystallisation from benzene–ethanol gave prisms, m. p. 216—218° (decomp.), identical with an oxidation product of 2,3-dimethylindole to be described in a later communication.

The above procedure was repeated using 2,3-dimethylindole (10 g.) and 1 or 2 equiv. of dichlorocarbene (see Table 1); yields are based on the theoretical amount of dichlorocarbene available from the weight of sodium taken.

TABLE 1.

Reaction of 2,3-dimethylindole with dichlorocarbene from chloroform and ethanolic sodium ethoxide.

Run	1	2	3
Dichlorocarbene (moles)	1	1	2
Temperature	50°	60°	60°
2,3-Dimethylindole (% recovered)	58	52	49
3-Chloro-2,4-dimethylquinoline (% yield)	11·3	10·7	7·2
3-Dichloromethyl-2,3-dimethylquinoline (% yield)	13·1	12·9	8·7
Molar ratio of the quinoline to the 3*H*-indole	0·86	0·83	0·83

(b) *With dichlorocarbene* (1 *mole*) *from ethyl trichloroacetate and sodium methoxide.* 2,3-Dimethylindole was treated with dichlorocarbene (1 mole), generated by Parham and Schweitzer's method,[15] as follows. The dry powdered indole (10 g.) and sodium methoxide (3·84 g.) were suspended by vigorous stirring in olefin-free light petroleum (100 ml.) at room temperature in a water-bath. Ethyl trichloroacetate (10 ml.) in the same solvent (30 ml.) was added dropwise during 1 hr. and the mixture stirred at 15—18° for a further 18 hr. Samples (0·5 ml.) were removed after 1 and 18 hr., concentrated by evaporation, and analysed by thin-layer chromatography on Kieselgel G. (Merck). The chromatograms were developed with chloroform, dried, and irradiated with a mercury lamp. 2,3-Dimethylindole, 3-chloro-2,4-dimethylquinoline, 3-dichloromethyl-2,3-dimethyl-3*H*-indole, and ethyl 2,3-dimethylindole-1-carboxylate (see below) were present (R_F values and fluorescence) in both samples, together with a new substance (R_F *ca.* 0·85, pale yellow fluorescence). This substance was extracted from a large-scale chromatogram with chloroform; its infrared spectrum showed no absorption in the N–H region.

Water (100 ml.) was added to the stirred reaction mixture and the layers separated. The aqueous layer was extracted with ether and the combined ether–light petroleum solution was extracted with ice-cold 10% hydrochloric acid (5 × 50 ml.). Isolation as under (a) gave a yellow crystalline basic fraction (2·0 g.) and a dark crystalline non-basic fraction (10·3 g.). Careful examination of the former by infrared spectroscopy and thin-layer chromatography failed to reveal any basic product not already described, and of the latter revealed ethyl 2,3-dimethylindole-1-carboxylate, described below. None of the material with R_F *ca.* 0·85 and pale

[18] Grammaticakis, *Bull. Soc. chim. France*, 1953, 93.
[19] Beer, Donavanik, and Robertson, *J.*, 1954, 4139.

yellow fluorescence was detected in either fraction. The products were isolated quantitatively by chromatography as before (see Table 2, Run 4).

(c) *With dichlorocarbene (2 moles) from ethyl trichloroacetate and sodium methoxide.* Repetition of reaction (b) with 2 moles of the carbene precursors gave the indole-1-carboxylic ester in improved yield. The standard isolation procedure gave a basic fraction (4·1 g.) and a non-basic fraction (10·4 g.). Adsorption of the latter on active alumina (3·5 × 35 cm.) and elution with light petroleum (400 ml.) gave an orange oil (4·3 g.) which was distilled to give 2,3-dimethylindole (0·5 g.), b. p. 100—110°/1 mm. and an oil (3·4 g.), b. p. 146—147°/1 mm., which was redistilled to give *ethyl 2,3-dimethylindole-1-carboxylate* (3·0 g.), b. p. 109—110°/0·3 mm., n_D^{23} 1·5685 (Found: C, 72·2; H, 6·7; N, 6·7. $C_{13}H_{15}NO_2$ requires C, 71·9; H, 7·0; N, 6·5%); *picrate*, orange needles from ethanol, m. p. 90—90·5° (Found: C, 51·2; H, 4·0. $C_{19}H_{18}N_4O_9$ requires C, 51·1; H, 4·1%). This ester was identical (infrared, and mixed m. p. of picrate) with that synthesised from 2,3-dimethylindolylmagnesium iodide and ethyl chloroformate (below). The product analyses of this (Run 5) and similar reactions of dimethylindole (10 g.) in light petroleum are summarised in Table 2. In one run (Run 6) sodium methoxide was replaced by potassium t-butoxide and in another (Run 7) ethyl trichloroacetate was replaced by chloroform.

TABLE 2.

Reaction of 2,3-dimethylindole with dichlorocarbene in light petroleum.

Run	4	5	6	7	8 *
Temperature	15—18°	15—18°	15—18°	35°	15—18°
Dichlorocarbene (moles)	1	2	1	2	1
Ethyl trichloroacetate (ml.)	10	20	10	—	10
Chloroform (ml.)	—	—	—	15	—
Sodium methoxide (g.)	3·84	7·70	—	7·51	3·75
Potassium t-butoxide (g.)	—	—	7·85	—	—
2,3-Dimethylindole (% recovered)	62	14	22	50	>90
Ethyl 2,3-dimethylindole-1-carboxylate (% yield)	2	23	12	—	—
3-Chloro-2,4-dimethylquinoline (% yield)	9·6	9·7	6·2	8·2	0·9
3-Dichloromethyl-2,3-dimethyl-3*H*-indole (% yield)	4·6	2·45	15·2	2·7	0·3
Molar ratio of the quinoline to the 3*H*-indole	2·1	4·0	0·4	3·0	3·0

* Run 8 was carried out in the presence of 1 molar equiv. of cyclohexene.

(d) *With dichlorocarbene from sodium trichloroacetate.* 2,3-Dimethylindole was treated with dichlorocarbene (1 mole), generated by Wagner's method,[20] as follows. The dry powdered indole (10 g.) and sodium trichloroacetate (13 g.) were heated under reflux in 1,2-dimethoxyethane (100 ml.) under nitrogen for 20 hr. The solvent was removed in a rotary evaporator at 40°/15 mm. and its chloroform content was estimated by gas–liquid chromatography (dinonyl phthalate; 75°; flow rate 40 ml./min.) to be 6·0 ± 0·5 g. (*ca.* 70%) by comparison of peak heights with standard mixtures of chloroform (retention time 225 sec.) and 1,2-dimethoxyethane (retention time 300 sec.). The oily residue was treated in the standard way to give dimethylindole (4·0 g., 40%), 3-chloro-2,4-dimethylquinoline (3·24 g., 24%), and 3-dichloromethyl-2,3-dimethyl-3*H*-indole (1·48 g., 9·2%); the ratio of the quinoline to the 3*H*-indole being 2·6. In an otherwise identical reaction, using 1,2-dimethoxyethane as supplied without drying or purification, much more dimethylindole (70%) was recovered.

Dechlorination of 3-Chloro-2,4-dimethylquinoline (cf. ref. 21).—The chloroquinoline (500 mg.), hydrazine hydrate (5 ml.), and 10% palladised charcoal (180 mg.) were heated under reflux in absolute ethanol (50 ml.) for 20 min. More palladised charcoal (20 mg.) was added and the solution was boiling for a further 5 min., filtered, and evaporated. The residual oil was shaken with 2% aqueous sodium hydroxide and extracted with dichloromethane. The extracts were washed with water, dried, and evaporated, to leave an oil (260 mg.) identical (infrared) with authentic 2,4-dimethylquinoline, which on treatment with ethanolic picric acid gave the insoluble picrate (604 mg., 60%), m. p. and mixed m. p. with 2,4-dimethylquinoline picrate 198—199°.

Ethyl 2,3-Dimethyl-1-carboxylate.—Dry 2,3-dimethylindole (10 g.) in anhydrous ether (30 ml.) was added dropwise during 30 min. to a solution of methylmagnesium iodide, prepared from

[20] Wagner, *Proc. Chem. Soc.*, 1959, 229; Wagner, Kloosterziel, and S. van der Ven, *Rec. Trav. chim.*, 1961, **80**, 740.
[21] Mosby, *Chem. and Ind.*, 1959, 1348.

magnesium (1·7 g.) and methyl iodide (5 ml.) in ether (70 ml.), and boiled under reflux for 30 min. External heat was removed and ethyl chloroformate (redistilled, 7 ml.) in anhydrous ether (20 ml.) was added dropwise to maintain boiling. The mixture was boiled for 18 hr. and cooled, and saturated aqueous ammonium chloride was added with vigorous stirring and the layers separated. The aqueous layer was extracted with ether (2 × 50 ml.) and the combined ethereal solutions extracted with ice-cold 10% aqueous hydrochloric acid, washed with water, dried, and evaporated to give an oil (15 g.) which was adsorbed on active alumina (3·5 × 30 cm.) and eluted as follows: (*i*) Light petroleum (500 ml.) then ether (5%) in light petroleum (1 l.) gave a pale yellow oil (7·5 g., 50%) which was distilled to give ethyl 2,3-dimethylindole-1-carboxylate, b. p. 103°/0·1 mm., n_D^{22} 1·5690, identical with that obtained from the ethyl trichloroacetate reaction above. (*ii*) Ether (10%) in light petroleum (500 ml.) gave 2,3-dimethylindole (0·65 g.) containing a little 2-acetamidoacetophenone (infrared spectrum). (*iii*) Ether (50%) in light petroleum (500 ml.) then ether (500 ml.) gave a yellow oil (1·8 g.), unchanged on further chromatography, $\nu_{max.}$ 3410 (N–H), 1704 (ester C=O), 1626w, 1600m (aromatic), 1305, 1230 (acetate C–O), 1096, and 750 cm.$^{-1}$ (*o*-disubstituted benzene), which was largely unchanged on boiling with 10% methanolic potassium hydroxide.

In a similar reaction of 2,3-dimethylindolylmagnesium iodide with dichloroiodomethane [22] a small amount of a halogen-containing basic oil was obtained, whose infrared spectrum showed strong similarities to that of 3-dichloromethyl-2,3-dimethyl-3*H*-indole (including the absence of N–H absorption). However, the oil gave a picrate, m. p. 147—148° (Found: C, 41·25; H, 3·2; N, 11·7%) which depressed the m. p. of the picrate of this 3*H*-indole.

*Attempted Conversion of 3-Dichloromethyl-2,3-dimethyl-*3H*-indole into 3-Chloro-2,4-dimethylquinoline.*—To determine the efficiency of the chromatographic separation of these two compounds, a mixture (1·0 g. of each) was adsorbed on neutral alumina (2 × 38 cm.) and eluted as follows. (*i*) Ether (0—5%) in light petroleum (500 ml.) gave only the quinoline (0·92 g., 92%), and (*ii*) ether (10—20%) in light petroleum (500 ml.) gave only the 3*H*-indole (0·97 g., 97%). Very small amounts (1—2 mg.) of the quinoline could be readily detected in the appropriate fractions from its characteristic smell and crystalline form and by the formation of a very insoluble picrate.

(a) *With ethanolic sodium ethoxide under the ring-expansion conditions.* The 3*H*-indole (500 mg.) was heated with ethanolic sodium ethoxide [from sodium (160 mg.) in absolute ethanol (10 ml.)] at 65—70° for 6 hr. Removal of the solvent at 60°/15 mm., followed by acid extraction, gave an oily solid (470 mg.) which after chromatography on neutral alumina gave the unchanged 3*H*-indole (420 mg., 84%), m. p. and mixed m. p. 72—75°, and a dark oil, *A* (50 mg.), insoluble in light petroleum. None of the quinoline could be detected.

(b) *With ethanolic sodium ethoxide at* 100°. The 3*H*-indole (500 mg.) and ethanolic sodium ethoxide [from sodium (160 mg.) in absolute ethanol (10 ml.)] were heated together in a sealed tube at 100° for 5 hr. as described by Plancher and Carrasco.[11] Removal of the solvent at 60°/15 mm., followed by extraction with dichloromethane, gave an oily solid (495 mg.) which after chromatography on neutral alumina gave the unchanged 3*H*-indole (405 mg., 81%), m. p. and mixed m. p. 72—74°, and the oil *A* (70 mg.). In this, and in a repeat experiment at 105° for 15 hr., none of the chloroquinoline could be detected.

(c) *With potassium t-butoxide in 1,2-dimethoxyethane.* After heating the 3*H*-indole (500 mg.) and potassium t-butoxide (800 mg.) in 1,2-dimethoxyethane (30 ml.) under reflux for 15 hr. under nitrogen, none of the 3*H*-indole or the quinoline could be detected by the standard procedure. The sole product was a yellow viscous oil (300 mg.) which did not contain halogen and did not give a crystalline derivative with picric acid; it was not investigated further. However, in a separate experiment the chloroquinoline, treated identically, was recovered (*ca.* 90%).

Similarly, neither the 3*H*-indole nor the quinoline could be detected after treatment of the 3*H*-indole with n-butyl-lithium at 15° for 4 hr.

(d) *With silver nitrate in boiling acetonitrile.* The 3*H*-indole (500 mg.) and powdered silver nitrate (1·1 g.) were boiled under reflux in acetonitrile (15 ml.) for 12 hr. under nitrogen. A slight deposit of metallic silver (*ca.* 15 mg.) was produced. Removal of the solvent, followed by acid extraction of the residue and chromatography, gave the unchanged 3*H*-indole (130 mg., 26%) and no trace of the chloroquinoline. The non-basic products were not investigated.

[22] Auger, *Compt. rend.*, 1908, **146**, 1037.

(e) *With aqueous ethanolic potassium hydroxide.* The 3*H*-indole (3·0 g.) and potassium hydroxide (5·0 g.) were dissolved in ethanol (90 ml.) and water (35 ml.) and the solution boiled under reflux for 24 hr. under nitrogen. Excess of water was added, the ethanol evaporated, and the solution extracted with ether (5 × 50 ml.). The ethereal solution was washed with water, dried, and evaporated to give a red oil, *A* (2·6 g.), as obtained in reactions (*a*) and (*b*) above, which gave weak tests for a primary aromatic amine; it was mixed with acetic anhydride (2 ml.) and set aside overnight at room temperature. The excess of acetic anhydride was removed by a current of hot air and the remaining oil adsorbed on neutral alumina (2 × 20 cm.). Elution with ether (5%) in light petroleum (200 ml.) gave the 3*H*-indole (0·3 g., 10%), and ether (40%) in light petroleum (500 ml.) gave a yellow oil (2·26 g.), which was unchanged on further chromatography and is assigned the structure 2-*acetamido*-β-*chloro*-α-*methylstyrene* (Found: C, 63·0; H, 5·8. $C_{11}H_{12}ClNO$ requires C, 63·0; H, 5·8%), $\nu_{max.}$ 3270 (bonded N–H), 1664 (sec. amide C=O), 1605w, 1580m (conj. aromatic), 1518 (sec. amide), 802 (trisubstituted ethylene), 754 cm.$^{-1}$ (*o*-disubstituted benzene). The ultraviolet spectrum showed only very strong end-absorption. This compound was unsaturated and contained chlorine but did not react with aqueous ethanolic silver nitrate. Treatment of 2-acetamido-β-chloro-α-methylstyrene (1·2 g.) with cold concentrated sulphuric acid (15 ml.) for 6 hr. yielded a base (1·04 g.) which gave prisms of 4-*chloromethyl*-2,4-*dimethyl*-4H-3,1-*benzoxazine*, m. p. 75° (from hexane) (Found: C, 63·2; H, 5·45; Cl, 17·0; N, 6·95. $C_{11}H_{12}ClNO$ requires C, 63·0; H, 5·8; Cl, 16·9; N, 6·7%); *picrate*, needles, m. p. 143° (from ethanol) (Found: C, 46·75; H, 3·75; N, 12·5. $C_{17}H_{15}ClN_4O_8$ requires C, 46·5; H, 3·45; N, 12·8%). The infrared spectrum of the base showed no absorption in the N–H region and had $\nu_{max.}$ 1642 (conj. C=N), 1600, 1580m (aromatic), 1269 and 1255 cm.$^{-1}$ (αβ-unsaturated ether); $\lambda_{max.}$ 259 (3·87); $\lambda_{min.}$ 229 (3·28) mμ. This compound reacted only slowly with aqueous ethanolic silver nitrate, but gave an immediate reaction after storage for several weeks.

Discussion

This reinvestigation of Plancher and Carrasco's reaction [11] of 2,3-dimethylindole, chloroform, and ethanolic sodium ethoxide has entirely supported their structures for the two basic reaction products, 3-dichloromethyl-2,3-dimethyl-3*H*-indole (II) and 3-chloro-2,4-dimethylquinoline (III). The structure of the latter is confirmed by its spectral properties (in good agreement for a 2,3,4-trisubstituted quinoline [23]), by the preparation of some new derivatives, by dechlorination to 2,4-dimethylquinoline, and by the inertness of the chlorine to nucleophilic displacement. Thus the structure, 4-chloro-2,3-dimethylquinoline, is eliminated and none of this isomer could be detected in the reaction products; if the chloroquinoline arose by way of the 3*H*-indole (II), as suggested,[11] formation of this isomer would also be possible. More significantly, the structure of the other basic product, the 3*H*-indole (II), is confirmed by the absence of the N–H absorption to be expected for the dichlorocarbene adduct (VII), and by the presence of characteristic absorption at 1618w and 1587s cm.$^{-1}$ attributed to the 3*H*-indole aryl–N=C system (*e.g.*, see ref. 24). The ultraviolet absorption was also in better agreement with the 3*H*-indole (II) than the cyclopropane structure (VII) which has the indoline chromophore.[24] Furthermore, the structure of the corresponding difluoromethyl compound, which shows very similar infrared and ultraviolet absorption, has been established from its proton magnetic resonance spectrum (described in Part II, following paper).

With the 3*H*-indole structure for Plancher and Carrasco's intermediate confirmed, attention was directed to its reported [11] base-catalysed conversion into the quinoline (III), for which there appeared to be no mechanistic analogue. The intramolecular nucleophilic displacement of chloride by the nitrogen lone-pair, shown for the dichlorocarbene adduct

[23] Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1958; Knight, Wallick, and Balch, *J. Amer. Chem. Soc.*, 1955, **77**, 2577.

[24] Georgian, *Chem. and Ind.*, 1957, 1124; Evans, Lyle, Watkins, and Lyle, *J. Org. Chem.*, 1962, **27**, 1553; Witkop and Patrick, *J. Amer. Chem. Soc.*, 1951, **73**, 713, 1558, 2188.

[arrows in (VII)], is clearly not applicable to the 3-dichloromethyl-3*H*-indole system. The 3*H*-indole (II) into quinoline (III) transformation could not be repeated. Treatment of the 3*H*-indole (II) with ethanolic sodium ethoxide at 100° for 5 hr., as described by Plancher and Carrasco,[11] under the milder conditions of the ring-expansion experiments, or under more vigorous conditions, led to its recovery in high yield, together with a hydrolysis product, 2-acetamido-β-chloro-α-methylstyrene (XI). None of the quinoline (III) could be found, though trial experiments showed that a 1% yield would be readily detected, and we conclude that the alleged transformation [(II) ⟶ (III)] does not occur. Other attempts to effect this transformation, with potassium t-butoxide in 1,2-dimethoxyethane, with n-butyl-lithium in ether, and with silver nitrate in methyl cyanide, were unsuccessful (see Experimental section).

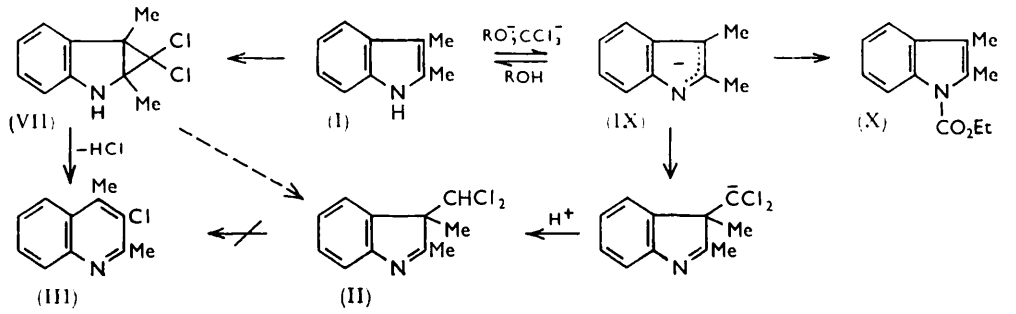
Plancher's dichloromethyl-3*H*-indole was prepared from 2,3-dimethylindole and chloroform and separated from the chloroquinoline by fractional crystallisation, a process which we find to be inefficient for separation of these bases. Thus his starting material may have been contaminated with the quinoline (III) which was recovered as its insoluble picrate, after treatment with sodium ethoxide.

Mechanism of the Reaction.—With this demonstration that the 3*H*-indole (II) was not an intermediate in the formation of the quinoline (III) and was not the adduct (VII), evidence for this adduct, which is presumed to be the precursor of the quinoline, was sought. The criteria for its presence were solubility in acid and infrared absorption of the N–H group. Conditions most favourable for its isolation appeared to be generation of dichlorocarbene by cleavage of ethyl trichloroacetate with an alkali-metal alkoxide in light petroleum at room temperature or below, in the presence of 2,3-dimethylindole. Careful chromatography of the basic products of this reaction yielded no such compound, however, and thin-layer chromatography during the reaction failed to detect it. Indeed, the adduct (VII) could not be isolated or even detected under any of our experimental conditions and it must be much less stable than the corresponding indene adduct (V). This is presumably because of the presence of the basic nitrogen atom facilitating the concerted displacement of chloride [(VII) ⟶ (VIII)] to give the highly stable quinolinium ion. However, isolation of the same products, (II) and (III), in the ethyl trichloroacetate reaction, and the ten-fold reduction in the yield of both in the presence of cyclohexene, are entirely consistent with the participation of dichlorocarbene in their formation. Further support was obtained by generating dichlorocarbene by thermal decomposition of sodium trichloroacetate in 1,2-dimethoxyethane containing dimethylindole; both the 3*H*-indole and the quinoline were again formed.

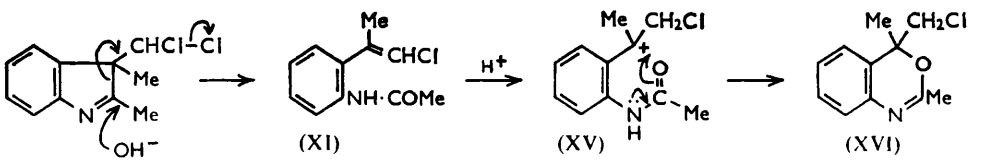
The results of generating dichlorocarbene under a variety of conditions are summarised in Tables 1 and 2 and in experiment (d); whilst the 3*H*-indole and the quinoline were formed in every case, the relative yields varied about ten-fold. No very precise significance can be attached to the product ratios quoted because of the complex nature of the reaction conditions, particularly with regard to variation of pH [and hence of the relative proportions of the indole (I) and its conjugate base (IX)] during a reaction, the differences amongst the various solvents in solvation of these species and the dichlorocarbene, and the varying degrees of heterogeneity of the reactions. Nevertheless one general trend of significance emerges. Formation of the 3*H*-indole (II) relative to the quinoline (III) is favoured the more strongly basic the reaction conditions. The product ratio of the quinoline to the 3*H*-indole is lowest (0·4) when the strongly basic potassium t-butoxide is used, higher (0·8) with sodium ethoxide in ethanol, and highest (2—4) with sodium methoxide suspended in light petroleum. This ratio is also high (2·6) under the so-called neutral conditions [20] of decomposition of sodium trichloroacetate in dimethoxyethane; the highest yield (24%) of the quinoline was obtained here, but the 3*H*-indole was also formed. Even if the latter arises, as seems most reasonable, by reaction of dichlorocarbene with the indolyl anion, and not with the neutral molecule, its formation under these " neutral " conditions is not unexpected. The carbene precursor is the very strongly basic trichloromethyl anion

which would readily abstract the indolic proton to give the indolyl anion (IX), in competition with its slow heterolysis to dichlorocarbene and chloride ion. The detection of a considerable amount of chloroform in this reaction, under anhydrous conditions, supports this view.

The simplest reaction scheme consistent with all our observations is considered to be as shown; similar schemes have been proposed in preliminary communications by Robinson [25] and ourselves.[26] The chloroquinoline arises only from addition of dichlorocarbene to the neutral indole (I) followed by ring-expansion of the labile adduct (VII).



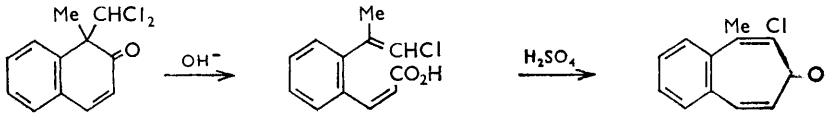
The dichloromethyl-3*H*-indole is formed by electrophilic attack of the carbene at the 3-position of the ambidentate indolyl anion (IX), and its formation by an alternative mode of opening of the cyclopropane ring of the adduct (VII) probably makes, at most, only a minor contribution. The variation in yields of the two products under different conditions does not support the idea of their formation by way of a common intermediate, either the indole–carbene adduct (VII) as suggested by Wynberg,[10] or its anion (VI) as suggested by Nakazaki.[13] No evidence was obtained for reaction of dichlorocarbene at position 1 of the indolyl anion (IX), to give the *N*-dichloromethyl or the *N*-formyl derivative. This parallels Nakazaki's observation [27] that reaction of the sodium salt of 2,3-dimethylindole with benzyl or alkyl halides, under heterogenous conditions, gave only the products of *C*-alkylation, characteristic of reactions between electrophilic species and indolyl–metal ion-pairs. In the reactions of dimethylindole with ethyl trichloroacetate the anion (IX) competed with the alkoxide ion in cleavage of the ester, to give only ethyl 2,3-dimethylindole-1-carboxylate (X) rather than ethyl 2,3-dimethyl-3*H*-indole-3-carboxylate. The same preference for reaction at the 1-position of the ambidentate nucleophile was found in the synthesis of the ester (X) from 2,3-dimethylindolylmagnesium iodide and ethyl chloroformate; these two reactions parallel the presumably bimolecular *N*-alkylation of the sodium salt of 2,3-dimethylindoles and methyl iodide.[27]



Base-catalysed Hydrolysis of 3-*Dichloromethyl*-2,3-*dimethyl*-3H-*indole* (II). Under the conditions of attempted conversion of the 3*H*-indole (II) into the quinoline (III) most of the former was recovered, but there was also formed a small amount of a neutral oil, $C_{11}H_{12}ClNO$, obtainable in good yield with aqueous ethanolic potassium hydroxide. On

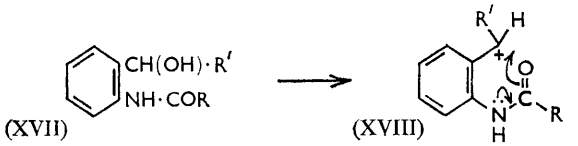
[25] Robinson, *Tetrahedron Letters*, 1962, 139.
[26] Rees and Smithen, *Chem. and Ind.*, 1962, 1022.
[27] Nakazaki, *Bull. Chem. Soc. Japan*, 1961, 334.

the basis of the analogy below, and its chemical and spectral properties, this was assigned the structure 2-acetamido-β-chloro-α-methylstyrene (XI). Some further hydrolysis to the corresponding amine also occurred but reacetylation of the acid-soluble product gave the



(XII) (XIII) (XIV)

amide (XI). This reaction is analogous to the recently reported [28] base-catalysed ring-opening of the " abnormal " Reimer–Tiemann product (XII) from 1-methyl-2-naphthol to form a β-chloro-α-methylstyrene (XIII). This styrene derivative underwent cyclodehydration in sulphuric acid to give the chlorobenzotropone (XIV).[28] Thus, in a two-stage reaction, ring-expansion of the dichloromethyl compound (XII), with elimination of hydrogen chloride, had been effected. The possibility of a similar route from the dichloromethyl-3*H*-indole (II) to the chloroquinoline (III), by way of the amide (XI), was envisaged independently by Wynberg [10] and ourselves. Although we have now shown that the 3*H*-indole (II) is not converted into the quinoline (III) under the various con-



(XVII) (XVIII)

ditions for ring-expansion, the amide (XI) was treated with cold concentrated sulphuric acid. No cyclodehydration to the quinoline (III) could be detected, however; instead the amide was isomerised to a base, m. p. 75°, which, on the basis of its mode of formation and spectral and chemical properties, is formulated as 4-chloromethyl-2,4-dimethyl-4*H*-3,1-benzoxazine (XVI). This would be formed by protonation of the double bond to give the stabilised benzyl carbonium ion (XV) followed by intramolecular nucleophilic attack by the amide oxygen atom, as shown. Support for this is found in the formation of other 3,1-benzoxazines by the acid-catalysed cyclodehydration of 2-acetamido- [29] and 2-benzamido-benzyl alcohols (as XVII) [30] presumably by way of the corresponding benzyl carbonium ions (as XVIII).

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King's College (University of London),
Strand, London W.C.2. [*Received, July 13th*, 1963.]

[28] Dodson, Lewis, Webb, Wenkert, and Youssefyeh, *J. Amer. Chem. Soc.*, 1961, **83**, 938.
[29] Gabriel and Posner, *Ber.*, 1894, **27**, 3509; von Auwers, *Ber.*, 1904, **37**, 2249.
[30] Patrick and Witkop, *J. Org. Chem.*, 1954, **19**, 1824; Singh, Andrews, and Keefer, *J. Amer. Chem. Soc.*, 1962, **84**, 1179.