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RADIOTRACER STUDY OF THE REACTION OF DICHLORO-CARBENE WITH DIMETHYLINDOLE

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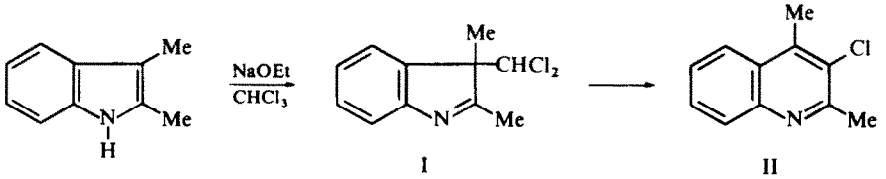
Abstract—The introduction of acetylchloride to the reaction of chloroform (C-14) and methyl lithium with 2,3-dimethylindole yields 3-dichloromethyl-2,3-dimethylindolenine (I) and the ring expansion product 3-chloro-2,4-dimethylquinoline (II). In addition the reaction mixture yields a solution, which after washing and purging with carriers has been shown by reverse isotope dilution techniques to yield I and II on alkaline hydrolysis. It is proposed that the solution contains a labile derivative of the reaction intermediate(s) of I and II. Consideration of the properties of this compound leads to the conclusion that both I and II could be derived from a common cyclopropane intermediate. The possibility that the indolenine is derived from an exocyclic methylene derivative of the indole is also considered.

PLANCHER and Carrasco[1] studied the reaction of chloroform with 2,3-dimethylindole and proposed that the indolenine (I) was intermediate in the formation of the quinoline ring expansion product (II). Nakazaki[2] proposed that both of the basic



products of this reaction were derived from a common cyclopropane intermediate. More recently, however, Robinson,[3] and Rees and Smithen,[4] have proposed that the ring expansion reaction proceeds via attack of dichlorocarbene on the indole 2,3-double bond, as suggested by Nakazaki, but the mechanism for the formation of the indolenine is attack of dichlorocarbene on the indolyl-3-anion.

To try to resolve this problem an attempt has been made to isolate the intermediate formed by reaction of labelled dichloro-carbene with 2,3-dimethylindole.

DISCUSSION

The existence of carbenes as reactive intermediates in some of the reactions involving the basic hydrolysis of chloroform is now widely accepted on the evidence of Hine.[5] Since the original work of Hine numerous other chemical systems thought to produce carbenes have been described and reviewed.[6,7] Dichlorocarbene was generated under a range of conditions by Rees and Smithen, and the products from

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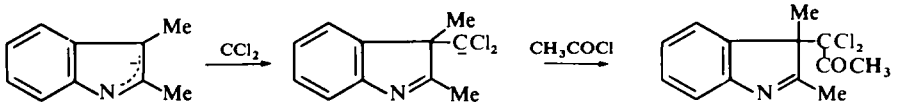
its reactions with 2,3-dimethylindole tabulated. The fact that the same basic products (3-dichloromethyl-2,3-dimethylindolenine and 3-chloro-2,4-dimethylquinoline) were produced under a variety of conditions, including the Reimer–Tiemann conditions used by Plancher and Carrasco, is justification for the hypothesis that both of these products are formed from the same reactive species—dichlorocarbene.

The formation of I and II from 2,3-dimethylindole as described in this paper can be considered as evidence that dichlorocarbene is also a major participant in this reaction. However, the mechanism of the reaction of the dihalocarbene with the 2,3-dimethylindole is open to debate.

Robinson,[3] and Rees and Smithen[4] were unable to convert the indolenine (I) to the quinoline (II). The possibility that the indolenine is an intermediate in the ring expansion product can therefore be discounted.

In the investigation described herein the presence of precursor(s) of I and II in solution A is unequivocally demonstrated. The addition of non-radioactive carriers of I and II to acid washed aliquots of solution A, and their subsequent quantitative removal to yield derivatives with relatively low specific activities, could be accounted for by the presence of small quantities of I and II not removed by the acid wash. A more probable explanation is that the precursor is unstable in acid solution, and is partially hydrolysed during the extraction of the carriers. The specific activities of the carriers recovered after alkaline hydrolysis of solution A were approximately ten times greater than those of the carriers used previously to purge the solution. This is very strong evidence for the presence of a true intermediate of I and II, or a derivative thereof, in solution A. Addition of a mixture of carriers to another aliquot of solution A, and their separation by chromatography after hydrolysis to yield radioactive derivatives of I and II is incontrovertible evidence that solution A contains radioactive precursor of both I and II. The failure of the precursor *per se* to withstand column chromatography is further evidence of its labile character.

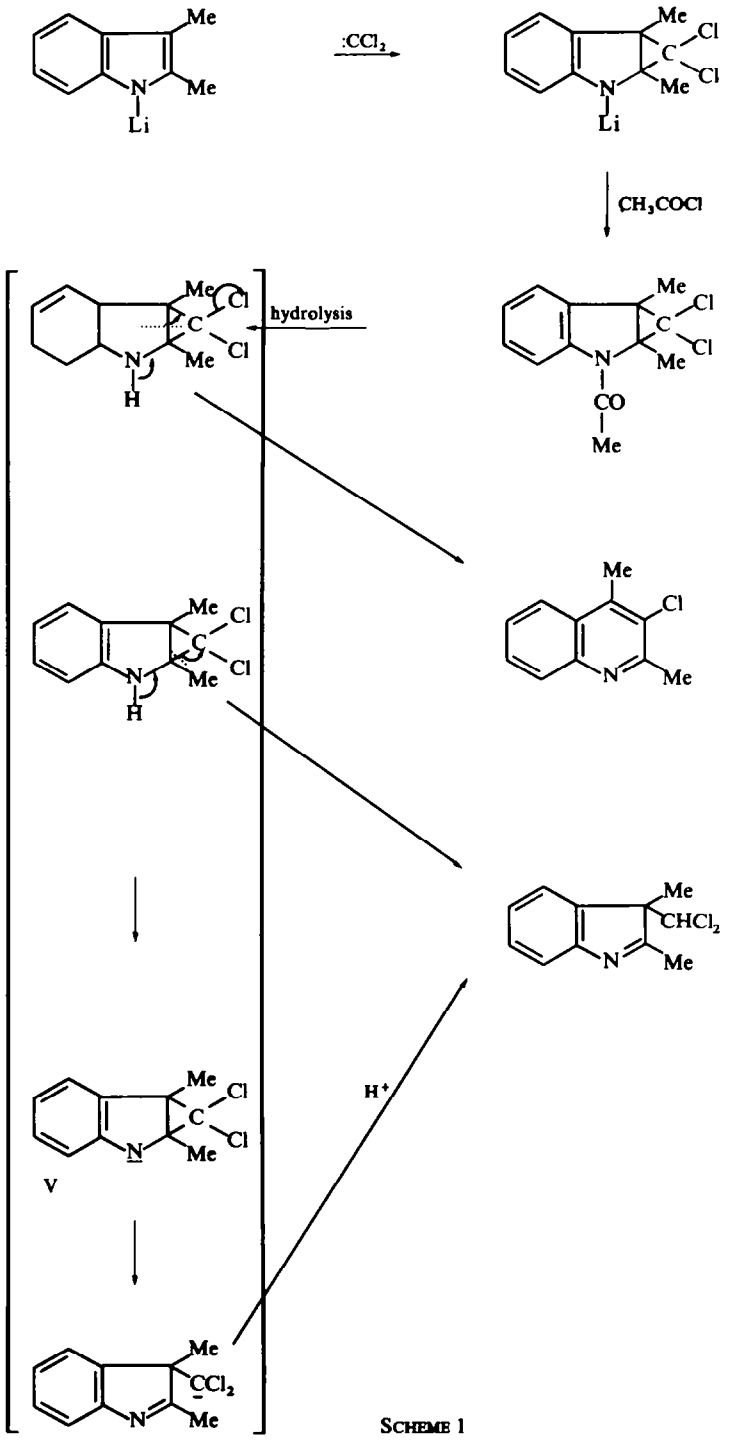
Methyl lithium reacts with indoles to form N-lithium derivatives and methane. If the lithium remains associated with the 2,3-dimethylindole during its reaction with dichlorocarbene the introduction of acetylchloride into the reaction mixture should yield the acetyl derivative of the intermediate. If the reaction resulting in the formation of the indolenine proceeds via the mesomeric indolyl anion (III), attack of carbene at the one position is unlikely to produce an intermediate that could logically be transformed into 3-dichloromethyl-2,3-dimethylindolenine. Attack of the carbene at the three position, as postulated by Rees and Smithen,[4] would yield the acetyl derivative represented by (IV). However, if the physical properties of this compound



III IV

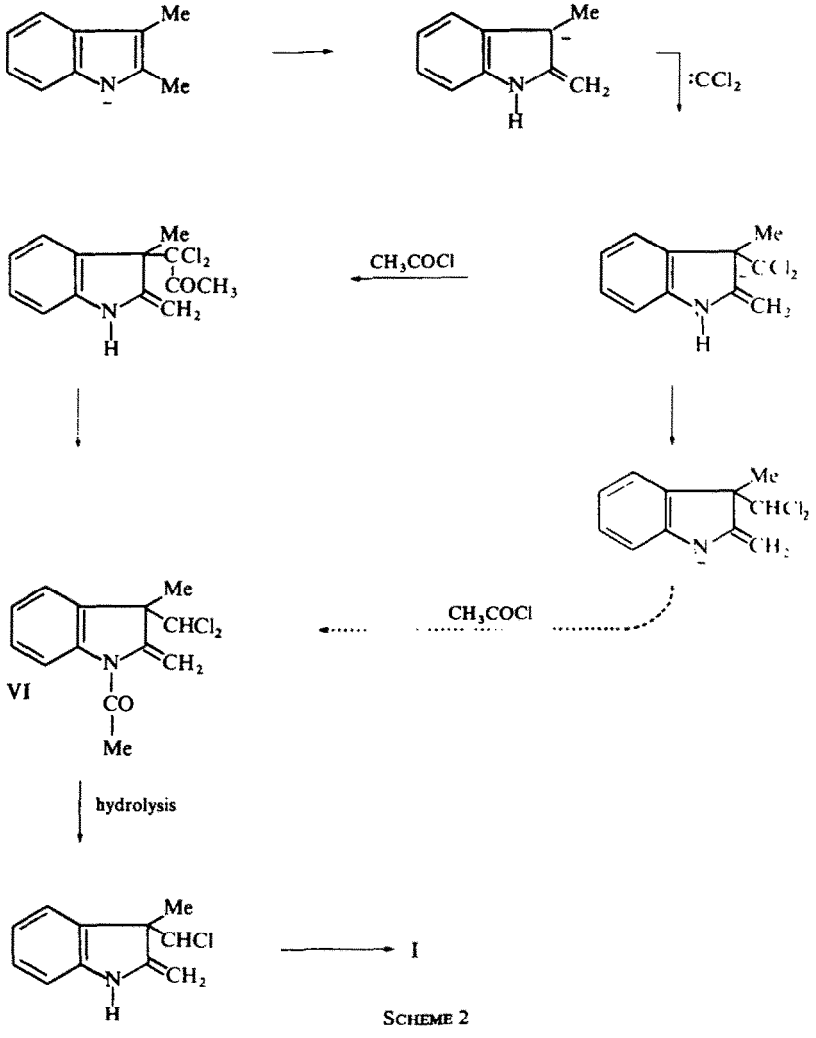
are in keeping with those of other known indolenines it would be basic, and therefore removed by acid extraction prior to hydrolysis. On these grounds its presence in the hydrolysed solutions can be discounted.

The cyclopropyl indolyl anion intermediate (V) proposed by Nagazaki does satisfy the experimental findings with labelled reagents, and the course of the reaction could follow Scheme 1.


Me
Me
N
Li
:CCl2
Me
Cl
C
Cl
Me
N
Li
CH3COCl
hydrolysis
CO
Me
H
V
H+
CHCl2
CCl2

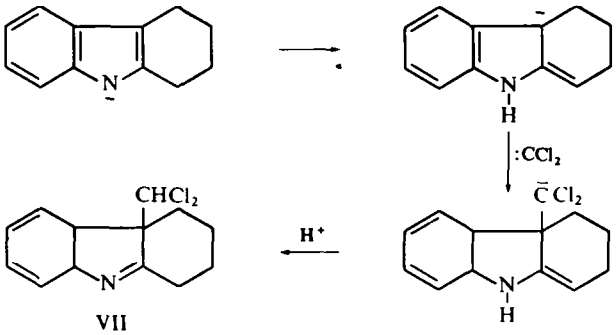
SCHEME 1

An additional neutral intermediate involving a 2-exocyclic methylene grouping on the indole (VI), however, could be involved in the formation of the indolenine. This postulate is strongly supported by an observation of Rees and Smithen[4] who deliberately looked for an indolenine but obtained only the ring expansion product when reacting dichlorocarbene with skatole (in which the 2 methyl group is absent.)



SCHEME 2

The formation of the indolenine could therefore proceed as shown in Scheme 2. If Scheme 2 is correct the presence of a methine group in the 2-position is essential for the formation of indolenines from indoles. Further supporting evidence for this suggestion is provided by the reaction of tetrahydrocarbazole with dichlorocarbene which yields the carbazolenine (VII) as the only basic product,[3] and could proceed via a similar mechanism (Scheme 3).



VII

SCHEME 3

EXPERIMENTAL

All radioactivity measurements were made in a coincidence liquid scintillator spectrometer.[8a] Volatile liquids were assayed by injection into weighed counting phials containing liquid scintillator and sealed with a rubber serum cap.[8b] Immiscible and quenching solids, (e.g. picrates) were mixed with cellulose powder and assayed by an oxygen flask combustion method.[8c] Counting efficiencies were measured with an "efficiency stick"[8d] and by "spiking" with hexadecane of known specific activity.[8b]

Chloroform (C-14). Carbon-14 labelled $CHCl_3$ was prepared by reacting acetone-1,3-C-14 with calcium hypochlorite.[8e]

3-Dichloromethyl-2,3-dimethylindolenine and 3-chloro-2,4-dimethylquinoline. These non-radioactive carriers were prepared by a modification of the method of Rees and Smithen.[4]

Reaction of 2,3-dimethylindole with carbon-14 labelled dichlorocarbene. This reaction is analogous to that of Closs and Schwartz.[9] 2,3-dimethylindole (commercial grade recryst. from EtOH–water; m.p. 89°; 21·0 g) was dissolved in dry ether (50 ml), and a soln of MeLi in ether (1·66N; 90·5 ml) added over 30 min without cooling. The addition caused the evolution of a gas (methane); the soln turned brick red in colour. A further quantity of dry ether (20 ml) was added to the reaction mixture which was then cooled to −40°. Carbon-14 labelled $CHCl_3$ (specific activity 10·5 μc/g; 17·93 g) was dissolved in dry ether (100 ml) and an aliquot of this soln (20 ml) was added to the reaction mixture over 30 min. The remainder of the soln was added over 2 hr simultaneously with that of a soln of MeLi in ether (1·66N; 90·5 ml, introduced from a separate dropping funnel). The reaction mixture was vigorously stirred throughout, and the temp maintained at −30°. A soln of acetyl chloride (23·6 g) in ether (50 ml) was next added over 30 min. Water (50 ml) was then rapidly introduced, and the ice cold ether layer (henceforth designated soln A) was immediately washed 10 times with water. The water washings were bulked with the acid aqueous phase and the whole basified with NaOH aq. The basic reaction products were extracted with ether which yielded a red oily solid (1·7 g). The oil was adsorbed on a neutral alumina (Brockmann activity 1·0) column (40 × 1·5 cm) and eluted with 100 ml vols of petrol (40–60°) containing progressively greater percentages of ether. The eluates containing 4% ether and 6% ether were combined and on evaporation gave an amber solid (0·5 g) that formed a picrate m.p. 210°(d) which did not depress the m.p. of authentic 3-chloro-2,4-dimethylquinoline picrate. The eluates containing 10% ether and 12% ether were also combined and gave an amber solid (0·25 g). This gave a picrate m.p. 160°(d) which did not depress the m.p. of authentic 3-dichloromethyl-2,3-dimethylindolenine picrate.

Treatment of the ether phase. Soln A from the above reaction mixture was made up to a total of 400 ml with ether. To a fraction of this soln (30 ml) was added inactive carrier 3-chloro-2,4-dimethylquinoline (72 mg). After dissolution this was extracted from the ether phase with ice cold dil HCl (the residual ether phase was designated solution B). The aqueous soln was made alkaline and the base quantitatively recovered and converted to the picrate. The picrate was recrystallized from EtOH–water (10 times) to constant specific activity (27 mμc/g). The residual ether soln (soln B) which was now purged of all possible radioactive 3-chloro-2,4-dimethylquinoline was evaporated, and a further quantity of non-radioactive 3-chloro-2,4-dimethylquinoline carrier (72 mg) added. The mixture was hydrolysed by refluxing for 16 hr with a soln of KOH (0·5 g) in water (1 ml) and EtOH (10 ml). The hydrolysis soln was then evaporated under reduced press and acidified. The acid soln was washed with ether, made alkaline with NaOH, and the base extracted and converted to the picrate. The picrate was recrystallized (10 times) to constant specific activity (340 mμc/g).

A further 30 ml of soln A was treated in a similar manner with two batches of non-radioactive 3-dichloromethyl-2,3-dimethylindolenine (265 mg each time). The specific activity of the picrate of the indolenine used to purge the ether soln was 39 mμc/g. The specific activity of the indolenyl picrate after alkaline hydrolysis was 241 mμc/g.

To provide an alternative method to fractional crystallization for the separation of the hydrolysis products, 20 ml of soln A were washed with ice cold 1N HCl (5 times) and evaporated with inactive 3-dichloromethyl-2,3-dimethylindolenine (265 mg) and 3-chloro-2,4-dimethyl quinoline (144 mg) carriers. The resultant residue was hydrolysed with alcoholic potash. After working up as before the recovered mixture of bases was adsorbed on a neutral alumina column and the components separated by elution with petrol–ether mixtures. The indolenine and quinoline were converted to their picrates each of which was recrystallized 10 times. The specific activities of the purified picrates were found to be 82 mμc/g and 107 mμc/g respectively.

An aliquot of soln A (200 ml) was evaporated and the residual black oil (10 g), adsorbed on an alumina column (50 × 2 cm) and eluted with 250 ml volumes of ether containing increasing percentages of acetone. Samples of each fraction collected were washed with acid and hydrolysed in the presence of 3-chloro-2,4-dimethylquinoline carrier. After working up as before the picrates from all fractions were found to contain no radioactivity.

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