Radiotracer Study of a Heterocyclic Ring-Expansion Reaction

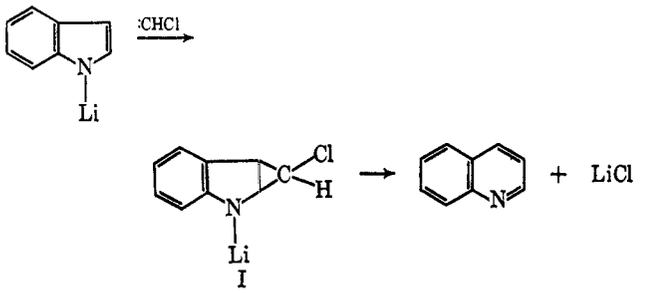
HORACE E. DOBBS

Research Laboratories,[1a] Reckitt & Sons Ltd, Kingston-upon-Hull, England

Received October 9, 1967

Indole reacts with methyllithium and methylene bromide to form quinoline and 1,2-dihydroquinaldine. The competitive rates of reaction of indole and skatole in this reaction have been compared using carbon-14-labeled methylene bromide reagent and reverse isotope dilution techniques to measure the ratio of the ring-expansion products. The substance isolated in an attempt to obtain the acetyl derivative of the reaction intermediate (in the formation of lepidine from skatole) was shown by carrier techniques to contain a lepidine precursor. The compound, which probably arises by hydrolysis of the anticipated intermediate on the chromatography column, is thought to be 2'-hydroxy-3-methylcyclopropano[2,3:2',3']indolenine, which yields lepidine by elimination of a molecule of water. The possibility that an isomeric aziridine is involved in the ring-expansion reaction is discounted as the new carbon atom (originally from the methylene bromide) enters the 3 position in the quinoline ring. The results support the proposal that the addition of a carbene or a carbenoid to the indole 2,3 double bond is the first step in the ring-expansion reaction.

The addition of methyllithium to a solution of indole in methylene chloride yields the ring-expansion product quinoline. Closs and Schwartz[1b] proposed that the reaction proceeds *via* attack of chlorocarbene on the indole 2,3-double bond resulting in the formation of a chlorocyclopropane intermediate (I) that subsequently eliminates lithium chloride to form the ring-expansion product. Several authors[2,3] have invoked the participation of carbenes in other reactions involving the conversion of indoles into quinolines.



The reaction of methylene bromide with methyllithium produces a species that reacts with indole and skatole to yield quinoline and lepidine, respectively.[4] These two quinolines react further with methyllithium to give 1,2-dihydro-2-methylquinoline and 1,2-dihydro-2,4-dimethylquinoline. The ring-expansion products are accompanied by unidentified indoles and a considerable quantity of polymeric material. These reactions have now been studied by ^{14}C tracer techniques.

The electrophilic character of halocarbenes has been postulated and confirmed by relative competitive reaction rate studies. Doering and Henderson[5] examined the reaction of dichlorocarbene with a range of olefins and observed an increase in reactivity with increasing substitution. Skell and Garner[6] observed a similar, although less pronounced, trend with dibromocarbene. Closs and Schwartz[7] measured the yields of chlorocyclopropyl derivatives obtained from a range of olefins in competitive reaction with monochlorocarbene generated from butyllithium and methylene chloride. Their results showed that the magnitude of the differences in reaction rate of chlorocarbene was lower than that of dichlorocarbene. Thus far no comparable study has been reported with bromocarbene.

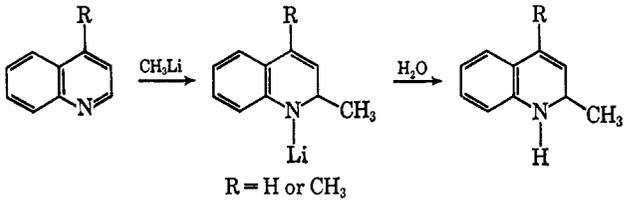
If a true carbene is involved in the ring expansion reaction of indole with methylene bromide and methyllithium the rate of reaction of bromocarbene with skatole should be increased to an observable extent relative to indole by virtue of the electron-releasing properties of the methyl substituent adjacent to the double bond.

The relative rates of the competitive reactions can be expressed as in eq 1 where k_i and k_s are the rate

$$k_i/k_s = R_sP_i/R_iP_s \quad (1)$$

constants for indole and skatole, respectively; P_i and P_s are mole fractions of total ring expansion products; and R_i and R_s are the mole fractions of the competitive reagents, indole and skatole, respectively.

Such an equation applies only if (a) the reactants are present in excess and (b) the product ratio is not changed by further reactions. It is considered that these conditions are fulfilled in the rate study described herein. The low over-all yields of the ring expansion products and the recovery at the completion of similar experiments of considerable quantities of unchanged indoles imply that the competitive reagents are always present in excess. It might be argued, however, that condition b is not fulfilled as the first ring-expansion products react further with the methyllithium to form the corresponding dihydroquinaldine derivatives. The high yields obtained in the preparation of



R = H or CH_3

these subsequent transformation products *per se* (see Experimental Section) indicate that these reactions are virtually quantitative. The measurement of the total ring-expansion products from each indole therefore satisfies condition b.

The three values for k_i/k_s obtained in this study were variable, with a mean value close to unity. Other workers studying the reaction of bromocarbene have observed product dependence upon the reaction condi-

(1) (a) Part of this work was conducted at the U. K. Atomic Energy Research Establishment, Wantage, Berks, England. (b) G. L. Closs and G. M. Schwartz, *J. Org. Chem.*, **26**, 2609 (1961).

(2) B. Robinson, *Tetrahedron Lett.*, No. 4, 139 (1962).

(3) C. W. Rees and C. E. Smithen, *J. Chem. Soc.*, 928 (1964).

(4) H. E. Dobbs, *Chem. Comm.*, 56 (1965).

(5) W. E. Doering and W. A. Henderson, *J. Amer. Chem. Soc.*, **80**, 5274 (1958).

(6) P. S. Skell and A. Y. Garner, *ibid.*, **78**, 5430 (1956).

(7) G. L. Closs and G. M. Schwartz, *ibid.*, **82**, 5723 (1960).

TABLE I

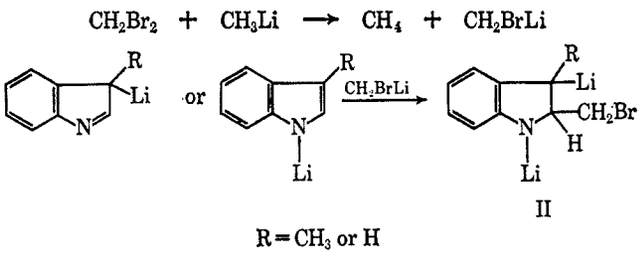
SUMMARY OF COMPETITIVE REACTION RATE STUDIES OF INDOLE AND SKATOLE WITH METHYLLITHIUM AND ^{14}C-LABELED METHYLENE BROMIDE

Experiment	Reactants, mmol: Methylene bromide	Methyllithium	Indole	Skatole	% yield of products (based on methylene bromide): Quinoline	Lepidine	1,2-Dihydroquinaldine	1,2-Dihydro-2,4-dimethylquinoline	Total basic products	k_s/k_i
1	16.4	49.2	8.2	8.2	0.071	0.116	0.019	0.045	0.25	1.8
2	20	60	10	10	0.042	0.033	0.061	0.064	0.20	0.9
3	30	180	30	30	0.207	0.186	0.087	0.088	0.57	0.9
									Mean	1.2

tions.[8] It is possible, therefore, that the variation of the individual values for k_i/k_s (Table I) can be attributed to changes in experimental conditions. The over-all lack of discrimination could be due to the low stability of bromocarbene relative to dibromocarbene (*cf.* chlorocarbene). This result may also be explained in terms of a "carbenoid" intermediate.

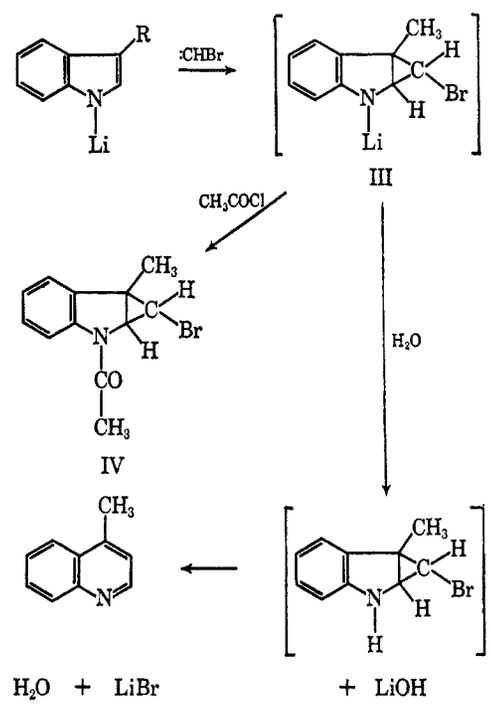
Closs and his coworkers,[9-11] postulated the involvement of "carbenoids" in reactions involving alkyllithium compounds, but were unable to confirm their existence by the isolation of derivatives. However, trichloromethyllithium[12] and dichloromethyllithium[13a] were subsequently prepared by other workers at low temperature.

On this evidence it is conceivable that the rate-controlling stage in the ring-expansion reactions discussed herein involves the addition of the carbenoid monobromomethyllithium to indolyllithium to form the adduct II. The same product (II) would be formed by carbenoid reaction with the lithium derivatives of both mesomeric indolyl anions. If bromomethyllithium is involved in the ring-expansion reaction it is likely that it would be less electrophilic than the true carbene, and would be more susceptible to steric hindrance, thus accounting for the similarity of the rates of reaction of indole and skatole.



In a preliminary nonradioactive experiment a mixture of lepidine and 1,2-dihydro-2,4-dimethylquinoline was obtained when skatole was allowed to react with methylene bromide in the presence of excess methyllithium for a prolonged period. As lepidine reacts rapdily with methyllithium to form 1,2-dihydro-2,4-dimethylquinoline it was concluded that a metastable intermediate was present in the reaction mixture, and that this compound was converted into the quinoline during the final hydrolysis stage.

In an attempt to produce a stable derivative of the possible anticipated intermediate (III), acetyl chloride was introduced into a reaction conducted with ^{14}C-labeled methylene bromide.[13b] Lepidine carrier was added to a



solution of a substance isolated from this reaction mixture. The lepidine was recovered, converted into the picrate, and after five recrystallizations was shown to be virtually inactive. The lepidine carrier added to another portion of the same solution, that was hydrolyzed with alcoholic potash, became radioactive, thus providing incontravertible evidence for the existence of a lepidine precursor.

The yield of the lepidine precursor from this reaction was very small, however, and it was necessary to repeat the experiment to obtain a sufficient amount of the compound for elemental and spectrophotometric analysis. The combined products were purified by repeated column chromatography, and effluent fractions containing the precursor were identified by hydrolsysis of an aliquot with alcoholic potash in the presence of lepidine carrier. Despite repetition of the experiment, the quantity of intermediate isolated was sufficient only for ir and elemental (and group) analysis, which surprisingly showed it to contain no bromine and no acetyl.

(8) C. W. Jefford, R. Medary, and B. Waegell, Communication to the Chemical Society, Autumn Meeting, Brighton, Sept 1966, paper A19.

(9) G. L. Closs and L. E. Closs, *J. Amer. Chem. Soc.*, **81**, 4996 (1959).

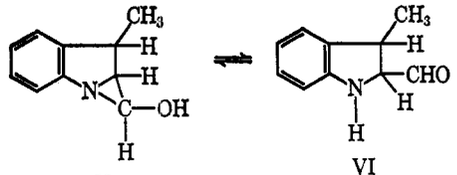
(10) G. L. Closs, *ibid.*, **84**, 809 (1962).

(11) G. L. Closs and L. E. Closs, *Angew. Chem. Intern. Ed. Engl.*, **1**, 334 (1962).

(12) W. T. Miller and D. M. Whalen, *J. Amer. Chem. Soc.*, **86**, 2089 (1964).

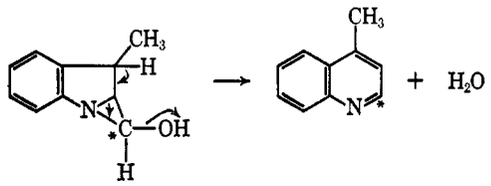
(13) (a) G. Kobrich, K. Flory, and W. Drischel, *Angew. Chem. Intern. Ed. Engl.*, **3**, 513 (1964). (b) Attempts to produce an amount sufficient for detailed analysis of the pure intermediate arising from the reaction of methylene chloride with methyllithium, and indole were not successful. The intermediate derived from [^{14}C]methylene chloride announced in a preliminary communication[4] has subsequently been shown to be impure.

A plausible composition for the product isolated, consistent with the ir and elemental analysis, is a mixture of the aziridine V and the tautomeric indoline aldehyde VI.

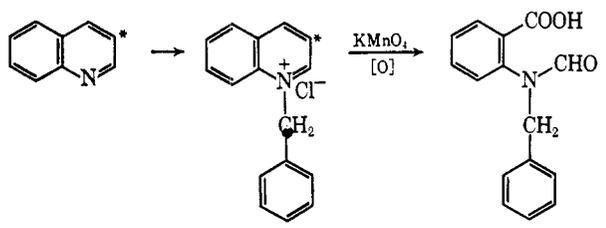


V VI

One possible mechanism for the formation of lepidine from structure V involves the loss of a molecule of water.

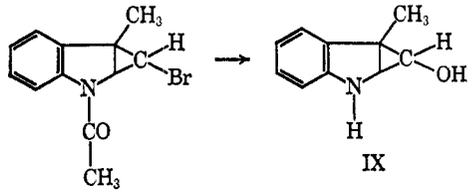


If this route is correct the labeled carbon atom would enter the quinoline ring in the 2 position. To investigate this possibility indole was treated with [^{14}C]-methylene bromide and methyllithium, and hydrolyzed with water. ^{14}C-Labeled quinoline was isolated from the reaction mixture, diluted with carrier, and converted into benzylquinolinium chloride (VII) which was recrystallized to constant specific activity. Oxidation of VII with potassium permanganate to yield nonradioactive N-benzyl-N-formylanthranilic acid (VIII) indicated that the radioactive carbon atom was in the 3 position of the quinoline ring.



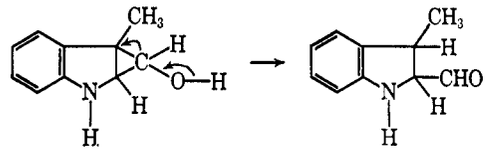
VII VIII + *CO_2

The formation of the ring-expansion product by ring opening and ring closure of the aldehyde VI under basic conditions is unlikely. It is probable, therefore, that the substance isolated is a mixture of the aldehyde VI and the isomeric cyclopropanol IX, which could be derived, by hydrolysis on the column, from the anticipated intermediate derivative IV. Rearrangement of



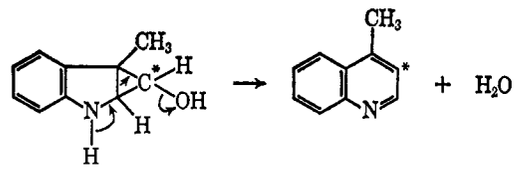
IV IX

the carbinol IX could lead to the formation of the aldehyde VI. Alternatively elimination of a molecule



VI

of water from the carbinol IX would lead to the formation of the ring-expansion product with the new carbon in the 3 position in the lepidine ring.



IX

It is concluded that the ring-expansion reaction of skatole with methyllithium and methylene bromide proceeds *via* addition of bromocarbene or bromomethyllithium to the indole 2,3 double bond. In an anhydrous medium lepidine is formed from the carbene (or carbenoid) adduct intermediate by the elimination of 1 or 2 mol of lithium bromide, respectively. The substance obtained in an attempt to isolate the acetyl derivative of the reaction intermediate is probably a mixture of an indoline aldehyde (VI) and a carbinol (IX) that is transformed to lepidine in boiling alcoholic potash by the elimination of a molecule of water.

The ring-expansion reaction was capricious. The use of radiotracer techniques, however, enabled the yields of selected products to be accurately measured. The use of labeled reagent also provided unequivocal evidence for the presence of small quantities of a ring-expansion precursor and enabled the chromatographic fractions containing it to be identified. The entry of the labeled carbon atom into the 3 position of the lepidine ring provided supporting evidence for the proposed mechanism of the reaction.

Experimental Section

Preparation of Nonradioactive Carriers. 1,2-Dihydroquinaldine.—Quinoline (6.45 g) dissolved in dry ether was added over 5 hr to a solution of methyllithium in ether (100 ml, 1 *M*) under reflux. The reaction mixture was cooled, hydrolyzed, and acidified with 5 *N* hydrochloric acid. Basification of the separated aqueous phase yielded an amber oil (6.3 g, n^{22}D 1.6125) corresponding to a yield of 87.5%. This was distilled at atmospheric pressure and the major fraction (bp 240°, n^{24}D 1.5969) gave a picrate, mp 187° dec.

Anal. Calcd for $C_{16}H_{13}N_4O_7$: C, 51.5; H, 3.49; N, 15.0. Found: C, 51.47; H, 3.38; N, 15.57.

1,2-Dihydro-2,4-dimethylquinoline.—Lepidine (14.3 g) in ether solution was treated with methyllithium (200 ml, 2 *M*) in a manner similar to that used for the preparation of 1,2-dihydroquinaldine to yield 11.5 g of a colorless oil: bp 142–144° (10 mm); n^{18}D 1.5984. It readily formed a picrate, mp 196° dec.

Anal. Calcd for $C_{17}H_{15}N_4O_7$: C, 52.8; H, 3.88; N, 14.5. Found: C, 52.85; H, 3.86; N, 14.59.

Preparation of ^{14}C-Labeled Reagent.—^{14}C-Labeled methylene bromide was prepared *via* bromoform from acetone[1,3-^{14}C] by adapting the methods described by Vogel[14] for the preparation of the nonradioactive compounds.

[^{14}C]Bromoform.—A 250-ml three-necked flask, containing a Teflon-coated magnet, was fitted with a reflux condenser and two dropping funnels, the stem of one of them reaching to the bottom of the flask. Aqueous 20% sodium carbonate solution

(14) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, Longmans, Green and Co. Ltd, 1959, pp 299, 300.

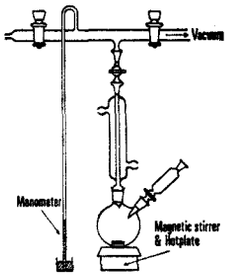


Figure 1.—Apparatus used for reaction-rate studies with methyllithium.

(50 ml) was placed in the flask which was cooled in liquid nitrogen and evacuated. Acetone[1,3-^{14}C] (6.6 g, specific activity 1.04 mCi/mol) was transferred to the flask by vacuum sublimation. The pressure was then rasied to atmospheric and the flask removed from the vacuum manifold and placed in an oil bath at 50°. Bromine (21 ml), placed in the long-stemmed funnel, was added to the warmed aqueous solution with vigorous stirring over a period of 3 hr. After 3 ml of the bromine had been added 180 ml of 11% aqueous sodium hydroxide was run into the reaction mixture, concomitantly with the bromine, at such a rate that the red color discharged if the flow of bromine was reduced. The bath temperature was maintained at 50° throughout the addition. The flask was then cooled in ice and the heavy bromoform layer separated. The aqueous phase was extracted twice with ether. The combined ether washings and bromoform were washed with water, dried with anhydrous calcium chloride, and fractionally distilled to give 19.98 g of the product: bp 149–152°; mp 4°; specific activity 0.47 mCi/mol.

[^{14}C]**Methylene Bromide.**—A 150-ml, two-necked flask containing a Teflon-coated magnet was fitted with a dropping funnel and a reflux condenser. Freshly prepared bromoform (19.0 g, specific activity 0.41 mCi/mol) was introduced into the flask which was placed in an oil bath. A sodium arsenite solution, prepared by dissolving arsenious oxide (8.9 g) and sodium hydroxide (16.8 g) in 50 ml of water, was introduced into the dropping funnel. A portion of the sodium arsenite solution (10 ml) was added to the bromoform with vigorous stirring, and the bath temperature slowly raised from 20 to 75°. The remainder of the arsenite solution was added over a period of 2.5 hr with the bath temperature maintained at 75°. When the addition was complete the bath temperature was raised to 85° and the mixture stirred for a further 2 hr. The reaction mixture was steam distilled, the methylene bromide was separated, and the aqueous layer extracted twice with ether. The combined ether extracts and methylene bromide were washed with water, dried over anhydrous calcium chloride, and fractionally distilled to give 7.5 g of the product: bp 96°; specific activity 0.39 mCi/mol.

Comparison of Reaction Rates.—The apparatus used in this study is shown in Figure 1. The flask was evacuated before the introduction of the reactants. Methane gas generated by the reaction of the indoles with methyllithium maintained an inert atmosphere (at atmospheric pressure) over the reaction mixture; the excess was allowed to escape *via* the manometer.

Experiment 1.—Indole (1.095 g) and skatole (1.23 g) dissolved in ether (30 ml) were slowly added to a solution of methyllithium in ether (10 ml, 5.62 *M*) and the mixture was heated under reflux for 90 min. [^{14}C]Methylene bromide (3.25 g, 19.14 mCi/mol) dissolved in ether (30 ml) was added over 3 hr. The mixture was stirred and heated under reflux for 19 hr. The flask was then cooled in ice and the reaction mixture hydrolyzed with water (25 ml) and acidified with concentrated hydrochloric acid. The separated ether layer was washed with water, and the washings were combined with the aqueous phase.

Accurately weighed quantities of single nonradioactive carriers (quinoline (0.55 g), lepidine (0.41 g), 1,2-dihydroquinaldine (0.42 g), and 1,2-dihydro-2,4-dimethylquinoline (0.69 g)) were added to known fractions of the total aqueous phase. Each solution was then basified and the basic products were extracted with ether. The extracts were evaporated, converted into picrate, and repeatedly recrystallized (up to 45 times) until the specific activity of the picrate reached a constant value.

The experiment was repeated twice using different quantities of reagents and modified conditions.

The results of all three experiments are contained in Table I.

Isolation of Intermediate.—An ether solution of methyllithium (66 ml, 5.0 *M*) was introduced into a flask connected to a vacuum manifold as in Figure 1. Skatole (8.78 g) dissolved in dry ether (100 ml) was added over 45 min with vigorous stirring and the mixture heated under reflux for 15 min. The flask was then cooled to 24° and methylene bromide (11.6 g, 0.43 mCi/mol) dissolved in dry ether (250 ml) added over 3 hr. The mixture was stirred for a further 1.5 hr, then cooled in ice and acetyl chloride (39.3 g) dissolved in ether (100 ml) added over 15 min. The reaction mixture was allowed to stand overnight at 0°. The ether layer was decanted and evaporated under reduced pressure. The residue was dissolved in acetone (5 ml), adsorbed on an alumina chromatography column (50 cm × 4 cm) cooled to 0°. The effluent was monitored for radioactivity by passage through a cell incorporating an inverted end-window geiger counter.[15] The column was eluted with 100-ml volumes of solvent of gradually increasing polarity. N-Acetyl skatole was eluted with 40–60° petroleum. The lepidine precurson was eluted with ether. Fractions containing the precursor were identified by hydrolysis of an aliquot with alcoholic potash in the presence of 0.5 g of lepidine carrier, which was subsequently converted into the picrate and recrystallized to constant specific activity. Fractions containing the lepidine precursor were evaporated and rechromatographed on alumina.

The above reaction was repeated twice, with modifications, and the lepidine precursor from each reaction was chromatographed twice. The fractions containing lepidine precursor from all of the reactions were combined, evaporated, and chromatographed two more times to yield an amber oil (~50 mg).

A portion of the oil was dissolved in ether (50 ml). Lepidine (0.2 g) was added to 25 ml of this solution. The lepidine was then extracted from the ether solution with dilute acid, converted into the picrate, and recrystallized five times. Assay of the picrate by oxygen flask combustion gave a very small count rate above background, which corresponded to a specific activity of <0.1 μCi/mol for the picrate. The remainder of the ether solution (25 ml) was evaporated in the presence of lepidine (0.2 g) and heated for 16 hr with a solution of potash (0.5 g) in water (1 ml) and ethyl alcohol (10 ml). The lepidine was subsequently extracted, converted into the picrate and recrystallized to constant specific activity (7.7 μCi/mol).

Analysis of the oil showed it to contain no acetyl and no bromine. The ir spectrum of the oil was measured as a thin layer between salts on a Perkin-Elmer "Infracord" spectrophotometer. The very strong absorption band at 3495 cm^{-1} in skatole that is attributed to the N–H stretching frequency was absent.[16] There were broad bands of medium intensity at 3350 and 1110 cm^{-1} that are indicative of a secondary OH. A strong carbonyl stretching band at 1660 cm^{-1} was also present. A band of medium intensity at 1020 cm^{-1} that could perhaps be attributed to a cyclopropane structure was also observed.

Anal. Found: C, 73.62; H, 7.09; N, 8.59; O, 10.7 (by difference).

Determination of the Position of Entry of the New Carbon Atom into the Quinoline Ring. Ring-Expansion Reaction.—Indole (7.25 g) was dissolved in ether and reacted with an equimolar quantity of methyllithium in ether solution (41 ml, 1.5 *M*). The reaction mixture was cooled in ice and methylene bromide (11.0 g, 118 μCi/mol) added concomitantly with another volume of methyllithium solution (41 ml, 1.5 *M*) over 2 hr with vigorous stirring. The reaction mixture was hydrolyzed with water and stirred for 10 min. It was then acidified with concentrated hydrochloric acid. Quinoline carrier (1.53 g) was added to the mixture and subsequently extracted, dried, and fractionally distilled to yield 1.11 g of the product: bp 237–241°; 10.6 μCi/mol.

Benzylquinolinium Chloride.—Quinoline (0.5 g) from the above reaction was diluted with carrier (2.5 g) and heated with benzyl chloride for 5 hr at 100°. The benzylquinolinium chloride was precipitated with ether and recrystallized from alcohol–ethylacetate to yield 2.6 g of pale pink crystals mp (~100) 170°. An aliquot (0.6 g) of this product was recrystallized ten times to constant specific activity. This purified compound, mp (100) 172°, had a specific activity of 0.84 μCi/mol.

(15) H. E. Dobbs, *J. Chromatog.*, **2**, 572 (1959).

(16) This band is not present in the spectrum of indole-3-aldehyde, and its absence is attributed to association of the N–H bond: D. G. O'Sullivan and P. W. Sadler, *J. Chem. Soc.*, 876 (1959).

Anal. Calcd for $C_{26}H_{14}NCl \cdot H_2O$: C, 70.3; H, 5.85; N, 5.1; Cl, 13.0. Found: C, 70.2; H, 5.65; N, 5.0; Cl, 13.0.

Oxidation.—The remaining benzylquinolinium chloride was oxidized to N-benzyl-N-formylanthranilic acid with potassium permanganate.[17]

Benzylquinolinium chloride (2.0 g) was dissolved in water (400 ml) and warmed to 30°. Potassium permanganate (4.12 g) dissolved in warm water (200 ml) was added over 2 hr with vigorous stirring. The reaction mixture was then made alkaline by the addition of a few pellets of solid potassium hydroxide and filtered. The filtrate was acidified with hydrochloric acid. The pale amber oil, that separated from the aqueous phase on acidification, solidified on standing. The solid was filtered and recrystallized ten times from ethyl alcohol to yield colorless granular crystals, mp 194°.

Anal. Calcd for $C_{15}H_{13}O_3N$: C, 70.6; H, 5.1; N, 5.5. Found: C, 70.5; H, 5.1; N, 5.5.

A sample of this purified product, dissolved in a dioxane-based scintillator, showed no detectable radioactivity.

Radioactivity Measurements.—Radioactivity measurements were made in a coincidence liquid scintillation counter.[18a] Nonquenching radioactive liquids were injected into weighed counting phials containing a suitable phosphor and sealed with rubber serum caps.[18b] Quenching liquids and solids (picrates) were burned in an oxygen flask combustion apparatus and the [^{14}C]carbon dioxide thus formed was dissolved in 2-phenylethylamine premixed with a liquid phosphor and injected into the flask.[18c] Counting efficiencies were measured with an "efficiency stick",[18d] and random samples were checked by "spiking" with a nonquenching standard.[18b]

(17) A. Claus and F. Glyckherr, *Chem. Ber.*, **16**, 1283 (1883).

(18) H. E. Dobbs: (a) U. K. Atomic Energy Authority Memorandum, AERE-M1075 (1962); (b) U. K. Atomic Energy Authority Memorandum, AERE-M1574 (1965); (c) *Anal. Chem.*, **35**, 783 (1963), and **36**, 687 (1963); (d) *Nature*, **200**, 1283 (1963).

Registry No.—1,2-Dihydroquinaldine, 1125-81-1; 1,2-dihydroquinaldine picrate, 15619-45-1; 1,2-dihydro-1,4-dimethylquinoline, 15619-46-2; 1,2-dihydro-2,4-dimethylquinoline picrate, 15619-47-3; benzylquinolinium chloride (VII), 15619-48-4; 1-benzyl-N-formylanthranilic acid (VIII), 15656-73-2; [^{14}C] bromo-form, 7825-2; [^{14}C]methylene bromide, 15619-50-6.

Acknowledgments.—Thanks are extended to Dr. W. A. Waters, F. R. S., Dr. K. W. Bentley, and Dr. G. T. Rogers for their advice and to D. G. Humphreys for technical assistance.

Aziridines. XVIII. Reactions of a 1,3-Diazabicyclo[3.1.0]hex-3-ene with Alkenes, Alkynes, and Diethyl Azodicarboxylate

HAROLD W. HEINE, AMOS B. SMITH, III, AND J. DAVID BOWER

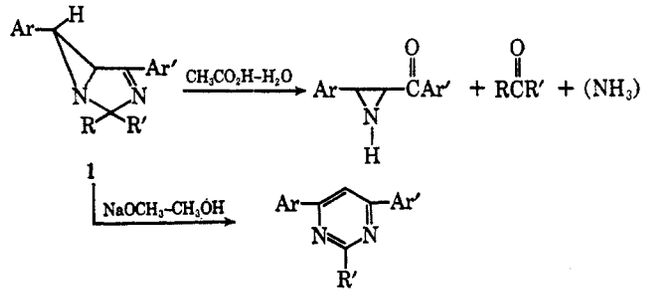
Department of Chemistry, Bucknell University, Lewisburg, Pennsylvania

Received October 17, 1967

Adducts of 2,2-dimethyl-4-phenyl-6-*p*-nitrophenyl-1,3-diazabicyclo[3.1.0]hex-3-ene with diethylacetylene dicarboxylate, diethyl fumarate, *cis*- or *trans*-dibenzoylethene, diethyl azodicarboxylate, and N-phenylmaleimide are formed in refluxing *p*-xylene. The reaction proceeds by carbon–carbon bond scission of the aziridine ring of the 1,3-diazabicyclo[3.1.0]hex-3-ene.

The synthesis of the previously unknown class of compounds, the 1,3-diazabicyclo[3.1.0]hex-3-enes (1), has been described recently.[1] Some of these compounds are converted in moist acetic acid into 2-aryl-3-aroylaziridines and ketones. Other 1,3-diazabicyclo-[3.1.0]hex-3-enes (where R = H) in methanol containing sodium methoxide rearrange and subsequently air oxidize into pyrimidines (Scheme I).

SCHEME I



We now have observed that in refluxing *p*-xylene 1,3-diazabicyclo[3.1.0]hex-3-enes form adducts with various alkenes, alkynes, and diethyl azodicarboxylate. The adducts are novel bicyclic or tricyclic systems and are formed by carbon–carbon cleavage of the aziridine ring. Recent work has demonstrated that carbon–carbon scission of the aziridine ring occurs when 1,2,3-triarylaziridines,[2] 2-aroylaziridines,[3] 2,3-diaroylaziridines,[4] and 2,3-dicarbethoxyaziridines[5] are heated in inert solvents with alkenes and alkynes.

Results

Refluxing a *p*-xylene solution of 2,2-dimethyl-4-phenyl-6-*p*-nitrophenyl-1,3-diazabicyclo[3.1.0]hex-3-ene (2) and diethylacetylene dicarboxylate formed diethyl 3,3-dimethyl-5-(*p*-nitrophenyl)-1-phenyl-3H-pyrrolo-[1,2-*c*]imidazole-6,7-dicarboxylate (3) (Scheme II). The structure of 3 was confirmed by acid hydrolysis to 2-benzoyl-3,4-dicarbethoxy 5-*p*-nitrophenylpyrrole (4) and presumably acetone. The hydrolysis of the 3-imidazoline moiety of 3 is analogous to the acid hydrolysis of 3-imidazolines to form α-amino ketones, ketones, and ammonium chloride[6] and of 1,3-diazabicyclo[3.1.0]-hex-3-enes to form 2-aryl-3-aroylaziridines and ketones.[1] The structure of 4 was assigned by means of an independent synthesis involving the addition of *trans*-2-*p*-nitrophenyl-3-benzoylaziridine (5) to di-

(1) H. W. Heine, R. H. Weese, R. A. Cooper, and A. J. Durbetaki, *J. Org. Chem.*, **32**, 2708 (1967).

(2) H. W. Heine and R. E. Peavy, *Tetrahedron Lett.*, 3123 (1965); H. W. Heine, R. E. Peavy, and A. J. Durbetaki, *J. Org. Chem.*, **31**, 3924 (1966).

(3) A. Padwa and L. Hamilton, *Tetrahedron Lett.*, 4363 (1965); A. Padwa and L. Hamilton, *J. Heterocyclic Chem.*, **4**, 118 (1967).

(4) R. Huisgen, W. Scheer, G. Szemies, and H. Huber, *Tetrahedron Lett.*, 397 (1966).

(5) R. Huisgen, W. Scheer, and H. Huber, *J. Amer. Chem. Soc.*, **89**, 1753 (1967).

(6) G. Kirchner, *Ann.*, **625**, 98 (1959).