[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, UNIVERSITY OF CHICAGO]

THE CONVERSION OF QUATERNARY PYRROLIDINIUM SALTS TO OPEN-CHAIN DIAMINES

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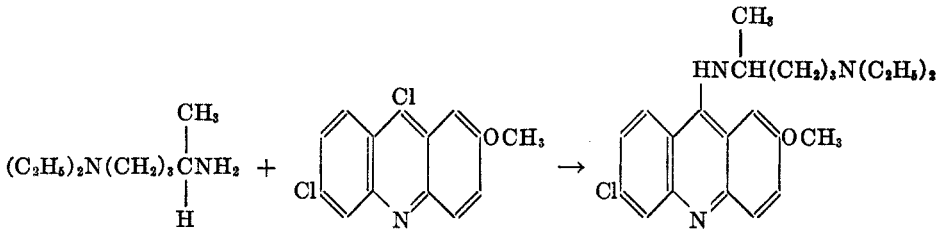
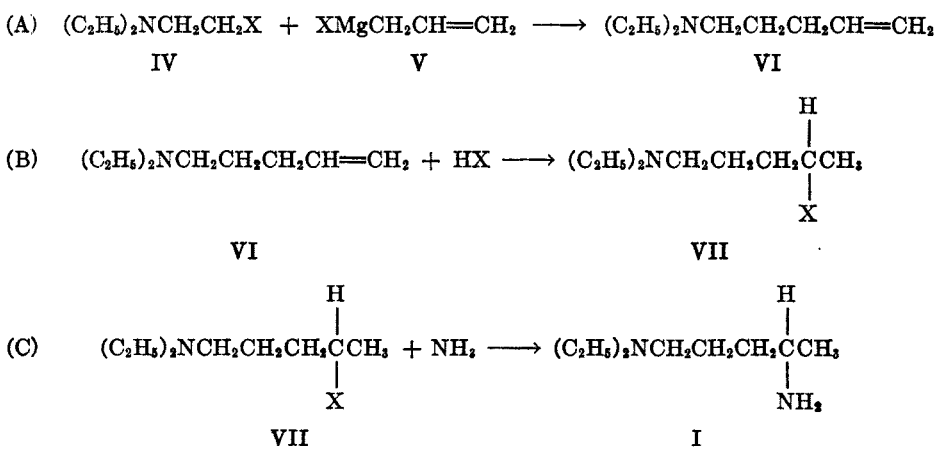
Atabrine (III), the most useful synthetic antimalarial now known, is formed by the reaction of 1-diethylamino-4-aminopentane (I) on 2-methoxy-6,9-dichloroacridine (II).



I II III

The reaction is a general one and many different primary-tertiary diamines may be used in place of (I). These, when coupled with (II), form compounds (hereafter referred to as atabro derivatives) analogous to (III) in structure but of varying antimalarial potency. The preparation of (II) and its condensation with a diamine analogous to (I) offer no great difficulties. The present methods for preparing diamines like (I) are, however, by no means satisfactory.

The work here described was, therefore, undertaken in the hope of improving the synthesis of (I) and related compounds. The reactions planned (A, B, and C) were the following, where X is any halogen atom.

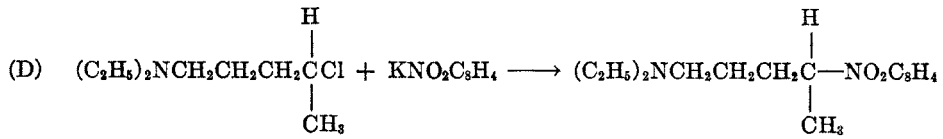


Since various halogenated tertiary amines might be used in place of (IV) and various substituted allyl Grignard reagents in place of (V), there was reason to

hope that the synthesis outlined might be developed into a fairly general method for preparing primary-tertiary diamines.

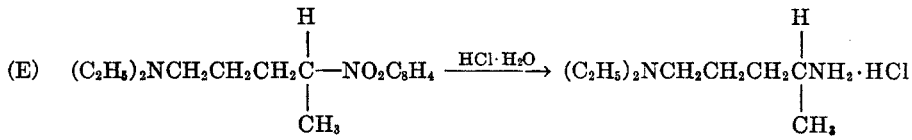
Reaction (A) proved easy to carry out. Contrary to literature reports, no difficulty was experienced in condensing β-chloroethyldiethylamine (IV) with allylmagnesium chloride (V), in spite of the low solubility of the latter compound in organic solvents. Reaction (B) also runs very smoothly. If a solution of (VI) in concentrated hydrochloric acid is saturated with hydrogen chloride, the addition reaction at room temperature is complete within 36 hours.

Reaction (C), on the other hand, proved quite difficult to handle. Liquid ammonia failed to give the desired result. Sodamide, acetamide, hexamethylenetetramine, and urea were equally ineffective. Success in replacing the chlorine atom by an amino group was finally obtained by taking recourse to the Gabriel synthesis. The chlorinated amine (VII) was treated with potassium phthalimide, the intention being to carry out the following reaction:



VII VIII

The anticipated product (VIII) should be the phthalimido derivative of (I). It was expected that when this compound was treated with concentrated hydrochloric acid, phthalic acid and the hydrochloride of (I) would be obtained.



VIII Hydrochloride of I

As a matter of fact, the phthalic acid residue was easily split off from the product of reaction (D). But when the free base was recovered from the amine hydrochloride thus obtained, it proved to be not a single compound, but a mixture of two components.

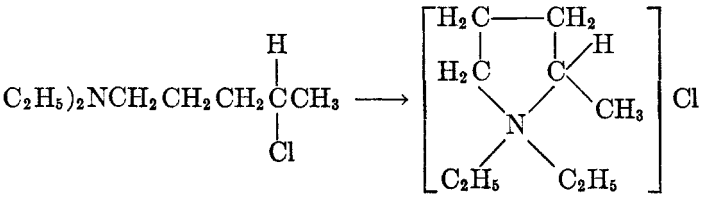
These two components (IX) and (X) were separated by distillation through a one hundred-plate column. Compound (IX), which formed about 10% of the mixture, was quickly identified (by its index of refraction and by the melting points of its picrate and atabro derivative) as (I). The analysis and titration value of (X) proved it to be a diamine isomeric with (I). But its index of refraction and the melting points of its picrate and atabro derivative showed conclusively that it was a distinct chemical compound.

It was, therefore, evident that at least one of the reactions (A, B, and D) had not proceeded in the manner indicated; reaction (E) seemed scarcely open to question. Various possibilities suggested themselves:

(a) In reaction (A), the coupling of (IV) and (V) might have been accompanied by a shift in the position of the double bond.
(b) In reaction (B), the addition of the halogen acid might not have proceeded as indicated; instead it might have taken place in the reverse direction.

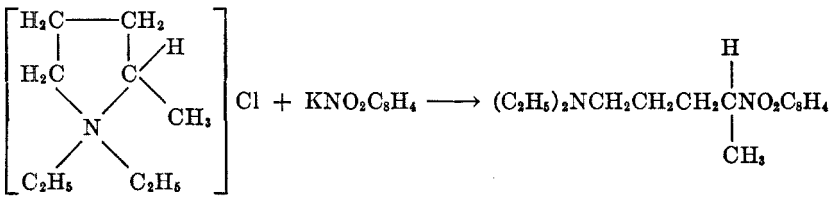
Careful investigation (see Experimental Part), however, showed that neither of these suppositions was correct. Both reaction (A) and reaction (B) were proved to have taken place in the manner indicated. The difficulty must, therefore, lie in reaction (D).

The following considerations support this latter hypothesis. Halogenated tertiary amines like (VII) are rather unstable compounds; they show a strong tendency to form cyclic quaternary ammonium salts. When (VII) undergoes such quaternization, the product is 1,1-diethyl-2-methylpyrrolidinium chloride

(F) 

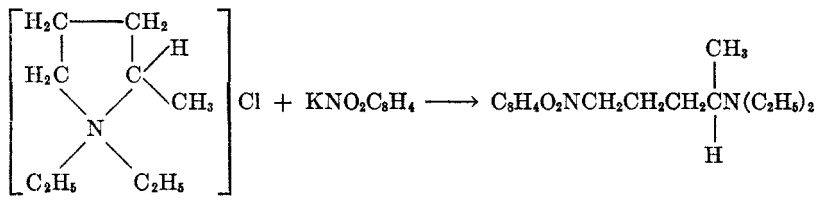
VII XI

(XI). Potassium phtnalimide might react in two distinct ways with (XI) to give an open-chain diamine. The splitting of the ring might take place either between the nitrogen atom and carbon atom 2 of the ring:

(G) 

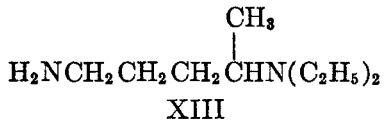
XI VIII

or between the nitrogen atom and carbon atom 5 of the ring:

(H) 

XI XII

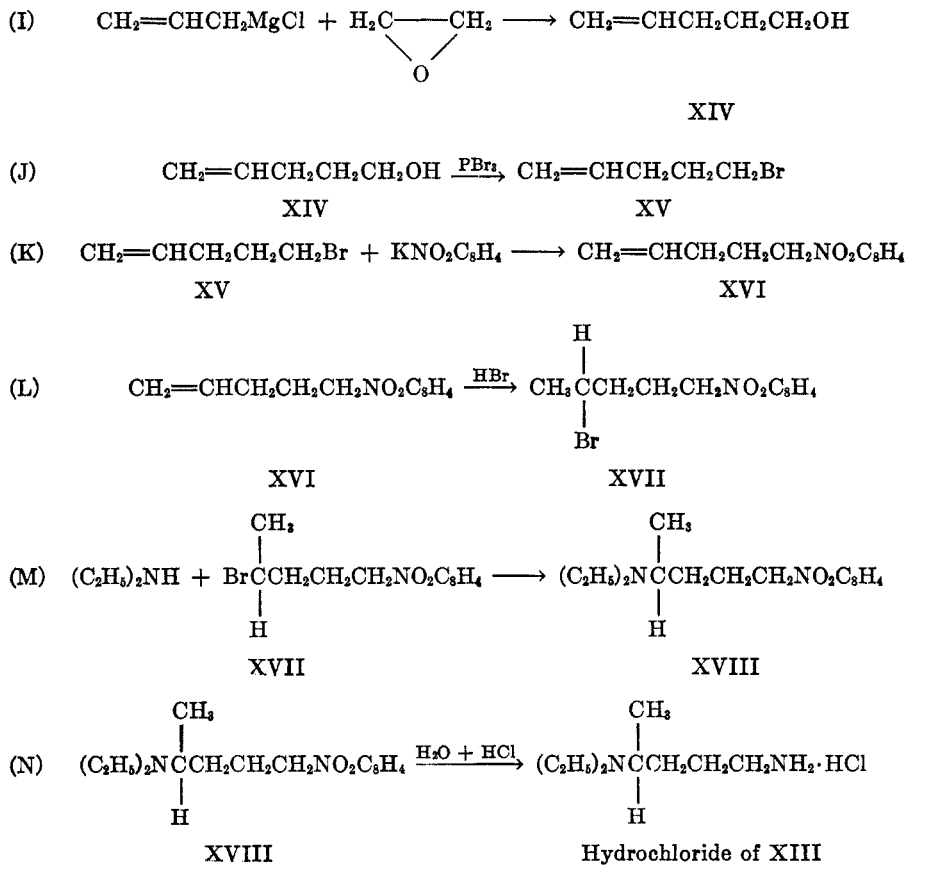
Compounds of the type (VIII) and (XII) are hereafter referred to as "phthalimido compounds." Hydrolysis of (VIII) would give (I). Hydrolysis of (XII), on the other hand, would give 1-amino-4-diethylaminopentane (XIII), isomeric with (I).



XIII

If the potassium phthalimide reacted on (XI) in both of the ways indicated, hydrolysis of the reaction product should give a mixture of (I) and (XIII). Since (VII) was treated with potassium phthalimide at a rather elevated temperature, it might well have been converted (at least to a considerable extent) into (XI) before the reaction with the phthalimide took place. Under these circumstances the product (X) [obtained along with the small amount of (I)] would in all probability have the structure given for (XIII). And such, indeed, proved to be the fact.

In order to establish the structure (XIII) for the product (X), it was necessary to synthesize (XIII) independently. This was done by the following series of reactions:



Of the intermediate compounds prepared in the above synthesis, (XIV) and (XV) were already known. The properties of the compounds obtained in re-

actions (I) and (J) agreed with those given in the literature. The analysis and unsaturation value of the product obtained in reaction (K) agreed accurately with those demanded by the formula (XVI). Compounds (XVII) and (XVIII) were identified by analysis only. The picrate of (XVIII) had the same melting point as one of the picrates isolated from the mixture obtained by treating with picric acid the mixture of "phthalimido compounds" obtained in the original synthesis. The final product (XIII) had the same boiling point and index of refraction as the product (X). Moreover, the picrates of compounds (X) and (XIII), as well as a mixture of the two all melted at 139–140°. Compounds (X) and (XIII) are, therefore, identical; and since the structure of (XIII) is established by its synthesis (reactions I–N), the structure of (X) is likewise determined. This structure lends strong support to the mechanism indicated in reactions (F), (G), and (H).

In order to check the conclusion thus reached, small amounts of (VII) were converted into quaternary salts. Both the quaternary chloride and the quaternary bromide were isolated in pure form and treated with potassium phthalimide. From the "phthalimido products," the free bases were isolated. The picrates of these clearly indicated that the free bases were mixtures. But the amount of material was too small to permit the isolation of any pure picrate save that of the major component. This proved to be (X) = (XIII) in both instances; but there is no reason to doubt that the minor component was (I), the same minor component isolated when large quantities of (VII) were treated with potassium phthalimide without preliminary isolation of the intermediate quaternary salt.

Chemically, the most interesting aspect of the work just recounted is the fact that it involves a novel method of preparing primary-tertiary diamines by the reaction of potassium phthalimide on quaternary pyrrolidinium salts. In order to determine the scope of the reaction, 1,1-diethylpyrrolidinium chloride, 2-methyl- and 2-phenyl-1,1-diethylpyrrolidinium halides and spiro(piperidine)-1,1-(2-methylpyrrolidinium) chloride, as well as quaternary halides derived from piperidine and pyridine, were treated with potassium phthalimide, sodium succinimide, sodium phenylacetylene and sodamide. The results obtained can be briefly summarized. Only quaternary pyrrolidinium compounds undergo ring-opening in the manner indicated in (G) and (H); the quaternary salts derived from pyridine or piperidine, when heated with potassium phthalimide, yield *N*-alkylphthalimide and (respectively) pyridine or *N*-alkylpiperidine. Only the alkali salts of phthalimide and succinimide open the pyrrolidine ring in such a way as to produce derivatives of diamines. Sodium phenylacetylene and sodamide open the ring to give unsaturated tertiary amines, a reaction similar to the Hofmann degradation. The low temperature (135°) at which these latter reactions occur may be of considerable importance for purposes of synthesis.

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EXPERIMENTAL

Preparation of allylmagnesium chloride. The preparation is carried out in an all-glass apparatus consisting of a three-liter, round-bottom, three-neck flask, an efficient stirrer, a reflux condenser and a dropping-funnel. The reflux condenser is connected through a drying tube to a water bubbler which permits the rate of formation of gaseous products to be observed. Magnesium turnings (80 g.) and dry ether (400 cc.) are placed in the flask, which is cooled in an ice-bath. The contents of the flask are vigorously stirred. Allyl chloride (230 g.) mixed with dry ether (400 cc.) is added through the dropping-funnel at a rate such that very little gas is evolved. Formation of the Grignard reagent begins soon, and is usually complete within 10 hours. The allyl Grignard reagent thus prepared is a white crystalline solid which forms a smooth suspension in the ether.

It has hitherto been generally believed (1) that a large excess of magnesium must be used to prepare allyl Grignard reagents, and that only allyl bromide yields a soluble reagent suitable for further reactions. Where allylmagnesium chloride has been employed (2), only a filtered and, therefore, very dilute solution of the compound has been used. Results here obtained indicate that Grignard compounds prepared from allyl and substituted allyl chlorides are indeed very slightly soluble in ethers or other solvents used in the preparation of Grignard reagents. But when such insoluble Grignard compounds react in suspension, the yields are better than when clear Grignard solutions of the corresponding bromides are used. Furthermore, these allyl and substituted allylmagnesium chlorides can be successfully prepared without the use of a large excess of magnesium.

Preparation of Unsaturated Amines (Reaction A)

Preparation of 1-diethylaminopentene-4. To the allylmagnesium chloride, formed as described, 1-diethylamino-2-chloroethane (330 g., 2.44 moles) is added at room temperature with continuous stirring. The addition through the dropping-funnel is conducted at such a rate that the heat of reaction keeps the ether gently boiling. (In case the reaction mixture becomes too thick to permit good stirring, dry ether may be added.) After the addition of the amine is complete, refluxing is continued for four hours. The flask is then cooled with ice, and, while the stirring is continued, carbon dioxide is blown over the surface of the reaction mixture to destroy most of the excess Grignard reagent. The pasty reaction product is then poured slowly onto ice (1 kg.) contained in a 5-liter flask. An excess of sodium hydroxide solution is then added, and the reaction product is removed from the alkaline mass by steam distillation. The 1-diethylaminopentene-4 is extracted with ether from the steam distillate. The ether extract is dried with anhydrous sodium sulfate or pellets of sodium hydroxide. After removal of the ether, the residue is distilled at reduced pressure. The yield is 85% of the amount calculated on the basis of the amine used. The same yield may be obtained if an ether solution of the allyl chloride and 1-diethylamino-2-chloroethane are mixed and introduced slowly into the flask containing magnesium covered with ether. If allylmagnesium bromide is used instead of allylmagnesium chloride, the yield of amine is considerably lower.

1-Diethylaminopentene-4 $(C_2H_5)_2N(CH_2)_3CH{=}CH_2$, is a colorless liquid, slightly soluble in water. Its boiling point is 156.4°/746 mm.; 81.6°/68 mm.; n_D^{20} 1.4310; d_{20}^{20} 0.8285. This unsaturated compound and the others that follow were analyzed for unsaturation by the bromate-bromide method. A 20% sulfuric acid solution was used as a solvent.

Anal. Calc'd for 0.2418 g. of $C_9H_{19}N$: Br, 0.2674 g. Found: Br, 0.2680 g.

The substance forms with ethyl iodide a quaternary salt which, after crystallization from acetone, melts at 147–148°.

The following tertiary amines have been prepared by the method described.

1-Diethylamino-4-methylpentene-4, $(C_2H_5)_2N(CH_2)_2C(CH_3){=}CH_2$, obtained in 75–80% yield from methylallylmagnesium chloride and 1-diethylamino-2-chloroethane; b.p. 83°/32 mm.; n_D^{20} 1.4377.

Anal. Calc'd for 0.2549 g. of $C_{10}H_{21}N$: Br, 0.2685 g. Found: Br, 0.2672 g.

1-Diethylaminohexene-5, $(C_2H_5)_2N(CH_2)_4CH{=}CH_2$, obtained in 75–80% yield from crotylmagnesium chloride and 1-diethylamino-2-chloroethane; b.p. 67–68°/31 mm.; n_D^{20} 1.4322.

Anal. Calc'd for 0.2695 g. of $C_{10}H_{21}N$: Br, 0.2774 g. Found: Br, 0.2753 g.

Tris(5-pentenyl) amine, $(CH_2{=}CHCH_2CH_2CH_2)_3N$, obtained in 90% yield from one mole of tris(2-chloroethyl)amine and three moles of allylmagnesium chloride; b.p. 90–91°/4 mm.; n_D^{20} 1.4618.

Anal. Calc'd for 0.1625 g. of $C_{15}H_{27}N$: Br, 0.3436 g. Found: Br, 0.3356 g.

1-Dimethylaminopentene-4, $(CH_3)_2N(CH_2)_3CH{=}CH_2$, obtained in 80% yield from allylmagnesium chloride and 1-dimethylamino-2-chloroethane (b.p. 118°/750 mm.; $n_D^{17.5}$ 1.4202). This base forms a methiodide which melts at 227–229°. Both the base and the methiodide had been previously prepared (3) by a process involving the Hofmann degradation of N-dimethylpiperidinium hydroxide.

1-Piperidinopentene-4, $C_5H_{10}N(CH_2)_3CH{=}CH_2$, obtained in 80% yield from 1-piperidino-2-chloroethane and allylmagnesium chloride; b.p. 94–95°/30 mm; n_D^{20} 1.4617. The hydrochloride and picrate of this unsaturated amine melt at 196° and 93–94°, respectively. v. Braun (4) prepared this compound by the Hofmann degradation of N-spirobispiperidinium hydroxide.

Addition of Halogen Acids to Unsaturated Amines (Reaction B)

Preparation of 1-diethylamino-4-chloropentane, $(C_2H_5)_2N(CH_2)_3\underset{\displaystyle Cl}{\overset{\displaystyle H}{\overset{|}{\underset{|}{C}}}}CH_3$. 1-Diethylaminopentene-4 (152 g.) is slowly added to 250 cc. of cooled concentrated aqueous hydrochloric acid. The mixture is cooled with ice, saturated with hydrogen chloride, and allowed to stand for 12 hours. Then it is again cooled, resaturated with hydrogen chloride, and allowed to stand at least 12 hours longer. At this point, a sample is withdrawn in order to test the completeness of the saturation by bromate-bromide titration. If practically no bromine is absorbed, the reaction is regarded as complete. Otherwise, the mixture is again saturated with hydrogen chloride and allowed to stand for another twelve hours. When saturation is complete, the excess acid is neutralized with sodium carbonate, and the base liberated with concentrated sodium hydroxide. During these steps, the reaction mixture is kept cool by immersing the reaction vessel in ice water. The free base is purified by vacuum distillation; b.p. 64–67°/5 mm. The yield of this substance is 90% of the amount calculated.

The following compounds were prepared by the method just outlined:

1-Diethylamino-4-methyl-4-chloropentane, $(C_2H_5)_2N(CH_2)_3\underset{\displaystyle Cl}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}CH_3$, obtained in 75% yield from 1-diethylamino-4-methylpentene-4; b.p. 64–65°/3 mm.; n_D^{20} 1.4459.

1-Piperidino-4-chloropentane, $C_5H_{10}N(CH_2)_3\underset{\displaystyle Cl}{\overset{\displaystyle H}{\overset{|}{\underset{|}{C}}}}CH_3$, obtained in 90% yield from 1-piperidinopentene-4; b.p. 88–92°/4 mm.

Preparation of Quaternary Pyrrolidinium Salts (Reaction F)

Preparation of the 1,1-diethyl-2-methylpyrrolidinium chloride. 1,1-Diethyl-2-methylpyrrolidinium chloride is easily prepared by heating a xylene solution of 1-diethylamino-

4-chloropentane to 140–150°. The quaternary salt precipitates as a white crystalline solid. The reaction is complete in 2–4 hours. The salt can be purified by collecting it on a filter, and washing it with dry ether. Such purification is unnecessary if the substance is to be used for the preparation of the phthalimido derivatives of primary-tertiary diamines.

The bromide of this base has also been prepared by addition of gaseous hydrogen bromide to 1-diethylaminopentene-5 and quaternization of the bromo derivative in ether solution.

The following compounds have also been prepared by the method just described:

Spiro(piperidine)-1,1-(2-methylpyrrolidinium) chloride. The bromide corresponding to this compound was prepared by v. Braun (5).

1,1-Diethyl-2-phenylpyrrolidinium chloride is prepared from 1-diethylamino-4-chloro-4-phenylbutane, which is obtained as follows. 1-Diethylamino-4-hydroxy-4-phenylbutane is prepared by the method of Marxer (6). A chlorine atom is introduced in the place of the hydroxyl group by heating the hydroxy compound with concentrated hydrochloric acid. The free base derived from the chloro compound thus formed is not purified but is merely dried *in vacuo* and quaternized by heating in xylene solution. It can be crystallized from acetone (m.p. 139–140°).

1,1-Diethylpyrrolidinium chloride was prepared from pyrrolidine by standard methods.

Reaction of Quaternary Pyrrolidinium Halides with Potassium Phthalimide (Reactions G and H)

1,1-Diethylpyrrolidinium chloride. 1,1-Diethylpyrrolidinium chloride (8 g.) is mixed with potassium phthalimide (10 g.) and 35 cc. of dry xylene. The mixture is stirred and heated to 155° (bath temp.) for 10 hours. The "phthalimido compound" (9 g., 64% yield) is obtained as a light yellow oil; b.p. 162–163°/0.3 mm.; n_D^{20} 1.5339.

Anal. Calc'd for $C_{16}H_{22}N_2O_2$: N, 10.46. Found: N, 10.35.

Its picrate melts at 121–122.5°.

Upon hydrolysis of this "phthalimido compound", a diamine hydrochloride is obtained. The picrate of this compound melts at 158–159°. The same melting point is reported (7) for the picrate of 1-diethylamino-4-aminobutane.

1,1-Diethyl-2-phenylpyrrolidinium chloride. 1,1-Diethyl-2-phenylpyrrolidinium chloride (4.2 g.) is mixed with potassium phthalimide (5 g.) and dry xylene (20 cc.). The reaction is carried out as previously described. The crude "phthalimido compound" is a clear, orange-yellow oil (yield 90%). This "phthalimido compound" when hydrolyzed with hydrochloric acid, gives phthalic acid and a diamine. The melting point of the picrate of this diamine is 185–186°.

1,1-Diethyl-2-methylpyrrolidinium chloride. In the following experiment the pyrrolidinium halide is formed *in situ*. 1-Diethylamino-4-chloropentane (171 g.) is mixed with 250 cc. of dry xylene in an all-glass, three-neck, one-liter flask provided with a stirrer and a reflux condenser. Dry potassium phthalimide (190 g.) is added, and the mixture is continuously stirred and gradually heated in an oil-bath to 130–140°. After a short time, a fairly violent reaction takes place which is merely the quaternization whereby 1,1-diethyl-2-methylpyrrolidinium chloride is formed from the free base. The bath temperature is then raised to 150–160° and the stirring is continued for 10–12 hours. At the end of this time, the reaction mixture consists of an orange-yellow liquid and a small amountof crystalline solid (potassium chloride). To the cooled mixture, water (200 cc.) and 2 *N* sodium hydroxide solution (50 cc.) are added to dissolve the potassium chloride and any phthalimide or phthalic acid which may be present; the whole mixture is then extracted three times with ether. The combined ether extracts are dried over anhydrous sodium sulfate. After the ether has been distilled from the extract, the xylene is distilled from the residue under reduced pressure. The xylene distillate contains a mixture of unsaturated tertiary amines which can be extracted from the xylene with dilute hydrochloric acid. This mixture of amines is mostly 1-diethylaminopentene-4 (identified by its ethiodide). The total amount of unsaturated amines recovered is about 10–15% of the 1-diethylamino-4-chloropentane used. A mixture of two "phthalimido compounds" remains after the xylene fraction is

removed. This mixture is a yellow oil which can be distilled below 1 mm. without decomposition. The yield of the two compounds is 80–85%.

The "phthalimido compounds" are soluble in dilute mineral acids, and can be recovered by treating the cold acid solution with alkali. If they are dissolved in dry ether and treated with dry hydrogen chloride, a mixture of crystalline hydrochlorides precipitates (m.p. 170–172°). Titration of these hydrochlorides with silver nitrate solution gives the correct value for $C_{17}H_{25}ClN_2O_2$.

Hydrolysis of the "Phthalimido Compounds" (Reaction E)

The "phthalimido compounds" (414 g.) prepared according to the method just described (Reaction D), are dissolved in 800 cc. of cooled concentrated hydrochloric acid. The clear solution is refluxed for 8 hours and cooled. The phthalic acid which precipitates is removed by filtration, and the filtrate is again refluxed for 8 hours. The additional phthalic acid which precipitates when the mixture is cooled is removed by filtration. The filtrate is concentrated *in vacuo* to remove the excess of hydrochloric acid and water. The viscous, semi-liquid residue is cooled, and the free bases are liberated by adding 40% sodium hydroxide solution and enough sodium hydroxide pellets to form a semi-solid mass. The diamines are extracted by stirring this mass with ether and decanting the supernatant ether extract. This procedure is repeated about 8 times. The combined ether extracts are dried over sodium hydroxide pellets, and the ether is removed by distillation. The remaining diamines are fractionated through a 100-plate column. Two fractions (a) and (b) are obtained. *Fraction (a)*: b.p. 101°/37 mm.; n_D^{20} 1.4435; 10% of the distillate.

Anal. Calc'd for $C_9H_{22}N_2$: N, 17.72. Found: N, 17.70.

The picrate of this substance melts at 134–136°. The melting point of a mixture of this picrate, with a picrate prepared from known 1-diethylamino-4-aminopentane showed no depression. Condensation of this diamine fraction with 2-methoxy-6,9-dichloroacridine gives a compound, the dihydrochloride of which melts at 244–245°‖ (decomp.); the melting point of a mixture of this substance with atabrine dihydrochloride (m.p. 244–245°) shows no depression.

Fraction (b): b.p. 104°/37 mm.; n_D^{20} 1.4475; 90% of the distillate.

Anal. Calc'd for $C_9H_{22}N_2$: N, 17.72. Found: N, 17.83.

The picrate of this compound melts at 139–140°. A mixture of the picrates of fractions (a) and (b) melts at 105–115°. The picrate of fraction (b) (m.p. 139–140°) and the picrate of 1-amino-4-diethylaminopentane (139–140°) (the synthesis of which is described later) give no melting point depression. Condensation of the fraction (b) with 2-methoxy-6,9-dichloroacridine gives a compound, the dihydrochloride of which crystallizes in fine yellow needles (m.p. 229° dec.) from a mixture of three parts acetone and one part alcohol. The sample analyzed was dried *in vacuo* at 60°. For the determination of the water the sample was dried *in vacuo* to constant weight at 105°.

Anal. Calc'd for $C_{23}H_{33}ClO \cdot 2HCl \cdot H_2O$: N, 8.56; H_2O, 3.67.
Found: N, 8.46; H_2O, 3.62.

Spiro(piperidine)-1,1-(2-methylpyrrolidinium) chloride. In the following experiment, the quaternary halide is formed *in situ*. 1-Piperidino-4-chloropentane (145 g.) is treated in the manner just described in dry xylene (200 cc.) and potassium phthalimide (140 g.). The crude "phthalimido compounds" (80% yield) are a clear, light orange oil. These "phthalimido compounds" are hydrolyzed with concentrated hydrochloric acid, and the free diamines isolated in the manner described. The diamines are distilled through a 20 cm. Vigreux column.

Fraction (a) b.p. 55–85°/6 mm.; about 10% of the total distillate.

Fraction (b) b.p. 87–89°/6 mm.; n_D^{20} 1.4763; about 85% of the total distillate. The picrate prepared from fraction (b), when crystallized from methanol, melts at 146.5–148°. The melting point of a mixture of this picrate with a picrate prepared from 1-amino-4-piperidinopentane (the synthesis of which is described later) shows no depression. Condensation of

the 1-amino-4-piperidinopentane thus obtained with 2-methoxy-6,9-dichloroacridine gives an "atabro" compound the dihydrochloride of which, upon crystallization from a mixture of acetone and alcohol, melts at 245° (dec.).

The syntheses hitherto described were carried out with 1-dialkylamino-4-chloropentanes as starting materials. Parallel reactions in which the starting materials were the pure quaternary pyrrolidinium chlorides or bromides (prepared by heating the 1-dialkylamino-4-halopentanes) have also been carried out. Every "phthalimido compound" or diamine thus obtained was identical with its analog obtained as already described (identity of physical constants and the melting points of the picrates and the atabro derivatives). The yields of the reaction products were at least as good as those already reported.

Reaction between 1,1-Diethyl-3-Methylpyrrolidinium Chloride and Sodium Succinimide

1,1-Diethyl-2-methylpyrrolidinium chloride (10 g.) was mixed with freshly prepared sodium succinimide (8.2 g.) and dry xylene (30 cc.). The mixture was heated to 150° (bath temp.) for 12 hours, continuously stirred, and then worked up in the manner previously described. The 5.5 g. of basic substances obtained were distilled below 70° at 100 mm. The distillate (2.5 g.) was identified by its index of refraction and the melting point of its ethiodide; it was mainly 1-diethylaminopentene-4. The non-volatile residue (2.5 g.) proved to be mainly 1-diethylamino-5 succinimidopentane. Hydrolysis of this "succinimido compound" gave succinic acid (1.1 g.; m.p. 185°) and the hydrochloride of the diamine. The melting point of the crude picrate prepared from the diamine was 132–135°. The compound, when recrystallized from alcohol, melted at 138–139°. The melting point of a mixture of this picrate with the picrate of 2-diethylamino-5-aminopentane showed no depression. There was no evidence to indicate the presence of a cyclic tertiary amine among the reaction products. Although the yield of "succinimido compounds" obtained in the above experiment is smaller than those obtained where potassium phthalimide was used, the courses of the two reactions are probably similar.

Reaction between 1,1-Diethyl-2-Methylpyrrolidinium Chloride and Sodamide

Freshly prepared sodamide (3 g.) was mixed with dry xylene (25 cc.) and 1,1-diethyl-2-methylpyrrolidinium chloride (25 cc.). The mixture was stirred, gradually heated to 150–155°, and kept at that temperature for 12 hours. The formation of a volatile base (probably methylamine) was observed during this period. Dry ether was added to the cooled mixture. The solid material (4.3 g.) was removed by filtration, and washed with dry ether. The basic substances were extracted from the clear, colorless filtrate with cold dilute hydrochloric acid. The bases were liberated from the acid solution with concentrated sodium hydroxide, and then extracted with ether. The ether extract was dried and the ether distilled off. The liquid residue was fractionated through a small Vigreux column.

Fraction (a) b.p. 63°/32 mm.; n_D^{20} 1.4307; (1.5 g.).

Fraction (b) b.p. 65–66°/32 mm.; n_D^{20} 1.4311; (3.7 g.).

Fraction (b) was identified as 1-diethylaminopentene-4; fraction (a) was identified as an unsaturated tertiary amine. It is probably 2-diethylaminopentene-4. No primary amines could be detected. The total yield of unsaturated tertiary amines was 82%.

Reaction between 1,1-Diethylpiperidinium Chloride and Sodamide

1,1-Diethylpiperidinium chloride (4.6 g.) was mixed with freshly prepared sodamide (2.6 g.) and dry xylene (20 cc.). The mixture was placed in a bath and heated first to 130° for 12 hours and then to 155° for 7 hours. During all this time it was continuously stirred. A volatile base was formed. The reaction mixture was worked up in a manner similar to that previously described. The extract contained only one detectable basic compound, 1-ethylpiperidine (2 g.). This compound was identified by its boiling point and the melting point of its picrate (168–168.5°). The melting point of a mixture of this picrate with pure 1-ethylpiperidine picrate showed no depression. No unsaturated tertiary amine and no primary amine could be detected.

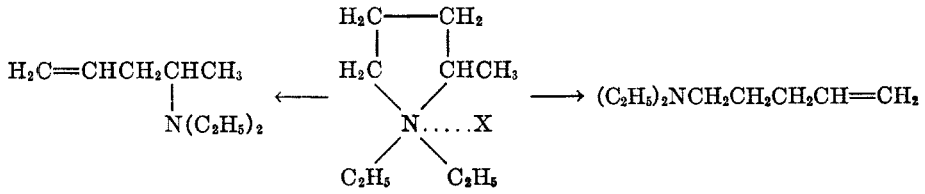
Reaction between 1,1-Diethyl-2-methylpyrrolidinium Chloride and Sodium Phenylacetylene

1,1-Diethyl-2-methylpyrrolidinium chloride (7.8 g.) was mixed with sodium phenylacetylene (6 g.) and dry xylene (25 cc.). The mixture was stirred and heated for 12 hours to 135° (bath temp.). The free bases were isolated in the manner previously described. Yield 90%.

Fraction (a) b.p. 143–151°/745 mm.; n_D^{20} 1.4313; (1.2 g.).

Fraction (b) b.p. 155–156°/745 mm.; n_D^{20} 1.4312; (4.2 g.).

The ethiodide prepared from fraction (b) melted at 146–147°. The melting point of a mixture of this ethiodide with the ethiodide prepared from 1-diethylaminopentene-4 showed no depression. The ethiodide prepared from fraction (a) melted at 160–162°. The structure of the unsaturated tertiary amine comprising fraction (a) was not established. This amine is probably an isomer of the one in fraction (b) since the pyrrolidine ring may be opened up in two ways.



Fraction (a) Fraction (b)

Reaction between 1,1-Dimethylpiperidinium Chloride and Sodium Phenylacetylene

1,1-Dimethylpiperidinium chloride (11.5 g.) was added to a mixture of freshly prepared sodium phenylacetylene (8.5 g.) and dry xylene (25 cc.). The mixture was stirred and heated to 150–160° (bath temperature) for 36 hours. The free bases were isolated in the usual manner. 1-Methylpiperidine (2 g., 25% yield) was identified by its picrate (m.p. 148–150°). The melting point of a mixture of this picrate with the picrate of pure 1-methylpiperidine (149–151°) showed no depression. No unsaturated base could be detected.

Reaction between 1,1-Dimethylpiperidinium Chloride and Potassium Phthalimide

1,1-Dimethylpiperidinium chloride (10 g.) was mixed with potassium phthalimide (14 g.) and dry xylene (35 cc.). The mixture was stirred and heated for 40 hours to 145° (bath temp.). The cooled reaction product was mixed with water (150 cc.) and 2 *N* sodium hydroxide solution (20 cc.); it was then extracted three times with benzene. The alkaline aqueous residue was acidified with 10% hydrochloric acid. The acidified mixture was at first clear; after being heated to 50–60° for two hours, it deposited phthalic acid (7 g.). This behavior indicated that, in the reaction, the phthalimide was probably converted to a phthalamic acid. No higher-boiling basic substance could be found in the aqueous mother liquor. The benzene-xylene extract was extracted with dilute hydrochloric acid. From this acid extract, the basic substances were liberated with cold 40% sodium hydroxide solution. 1-Methylpiperidine, the base thus obtained (yield 2.0 g.), was identified by its index of refraction (n_D^{20} 1.4378) and the melting point of its picrate (149–151°). The melting point of a mixture of this picrate with the picrate of 1-methylpiperidine (149–151°) showed no depression. N-Methylphthalimide (4 g.) was isolated from the benzene-xylene solution. It was identified by its melting point (136–137°); the melting point of a mixture with pure N-methylphthalimide showed no depression.

Reaction between Spiro-N-dipiperidyl Bromide and Potassium Phthalimide

Spirodipiperidyl bromide (16.5 g.) and potassium phthalimide (7.5 g.) were mixed with dry xylene (40 cc.). The mixture was stirred and heated to 155–165° (bath temp.) for 20 hours. A test made at this point on a small portion of the reaction mixture showed that no unsaturated compound had been formed. Consequently, the solvent was distilled off

and the residue was heated for 6 hours at 210°. Xylene (35 cc.) was again added, and the mixture heated 24 hours longer at 160–170°. After the mixture had been cooled, the solid crystalline material was removed by filtration and washed with dry ether. The yield of solid material was 15.5 g. It was identified as spiro-N-dipiperidyl bromide. This experiment indicates that quaternary nitrogen spirans with two six-membered rings, do not react with potassium phthalimide under the conditions used.

Reaction between 1-Methylpyridinium Chloride and Potassium Phthalimide

Dry 1-methylpyridinium chloride (12.5 g.) was mixed with 19 g. of potassium phthalimide and 30 cc. of dry xylene. The mixture was stirred and heated to 80–90° (bath temp.) for 8 hours. It turned brownish, even in the absence of air. For this reason, the reaction temperature was not raised above the point indicated. The mixture was worked up by a procedure similar to the one previously described. The only products identified were: N-methylphthalimide (3 g.) and pyridine (2 g.). The former was identified by its melting point, the latter by the melting point of its picrate.

Syntheses of Substances Mentioned in Reactions (I, J, K, L, M, and N)

Preparation of Pentene-1-ol-5 (XIV). The preparation is carried out in an all-glass apparatus, consisting of a three-liter, round-bottom, three-neck flask, an efficient stirrer, and a reflux condenser adapted for the use of dry ice and alcohol as a cooling agent. Two moles of allyl chloride are used to prepare allylmagnesium chloride in the manner previously described. An excess of dry ethylene oxide is then added at room temperature to the Grignard reagent. This addition, which is carried out with continuous stirring, is conducted at such a rate that almost no condensation of ethylene oxide in the reflux condenser is noticeable. After the addition is complete, the mixture is stirred at room temperature for 4 hours and then left to stand for 12 hours. It is then refluxed and stirred for two hours, cooled, and the reaction product decomposed by pouring it slowly onto ice (1 kg.). Acetic acid (20% sol.) is added until all the magnesium salts are dissolved. The mixture is then extracted four times with ether; the combined ether extracts are dried over anhydrous sodium sulfate. After removal of the ether by distillation, the residue is fractionated through a 100-plate column; b.p. 76.4°/60 mm.; n_D^{20} 1.4299. The yield is 60%, calculated on the basis of the allyl chloride used.

Pentene-1-ol-5 had been previously prepared in poor yield (14–22%) by other methods (8, 9). The method here described is not restricted to the preparation of pentene-1-ol-5, but is useful in the preparation of homologous unsaturated alcohols from substituted allyl halides and various epoxides.

Preparation of 5-Bromopentene-1 (XV). 5-Bromopentene-1 (9) is prepared by treating pentene-1-ol-5 with phosphorus tribromide in the presence of pyridine (b.p. 125–126°/760 mm.; n_D^{20} 1.4632).

Preparation of 5-phthalimidopentene-1 (XVI). The preparation is carried out in an all-glass, three-neck, round-bottom, 500-cc. flask provided with a stirrer and a reflux condenser. Potassium phthalimide (106 g.) is mixed with dry xylene (150 cc.) and 5-bromopentene-1 (82 g.). The mixture is stirred and gradually heated in an oil-bath to 150° (bath temp.). Heating and stirring are continued for 6 hours, during which period the bath temperature is raised to 160°. The reaction product is cooled and mixed with water (250 cc.) and 2 *N* sodium hydroxide solution (50 cc.). The mixture is extracted three times with ether, and the ether extract dried over anhydrous sodium sulfate. The solvents (ether and xylene) are removed by distillation, first under atmospheric and then under partly reduced pressure. The residue is an orange colored oil which distills at 155–157°/2 mm. The distilled phthalimido-5-pentene-1 forms colorless crystals. After being recrystallized from cold, low-boiling ligroin, it melts at 40°; the yield is 90%.

Anal. Calc'd for $C_{13}H_{13}NO_2$: N, 6.51. Found: N, 6.20.

Preparation of 2-bromo-5-phthalimidopentane (XVII). 5-Phthalimidopentene-1 (20 g.)

is placed in a bomb tube with dry hydrogen bromide (20 g.). The sealed tube is heated for 2 hours to 40° and allowed to stand at room temperature for 40 hours. The reaction product is extracted with ether. The ether extract is washed with cold sodium bicarbonate solution and with water; it is then dried with anhydrous sodium sulfate. The solvent is removed by distillation, and the reaction product is heated to 60–70° at 2 mm. for 4 hours to remove any volatile material. The 2-bromo-5-phthalimidopentane thus obtained is a light yellow oil. The yield is 98%. The compound crystallizes when cooled in a dry ice-alcohol mixture. It was analyzed by hydrolysis with 8% alcoholic sodium ethoxide and titration of the bromide ion thus formed.

Anal. Calc'd for $C_{13}H_{14}BrNO_2$: Br, 27.0. Found: Br, 26.80.

Preparation of 2-diethylamino-5-phthalimidopentane (XVIII). 2-Bromo-5-phthalimidopentane (10 g.) and dry diethylamine (20 g.) are heated to 90–100° in a bomb tube for 12 hours. The excess of free diethylamine is removed by evacuating the bomb tube at room temperature. The residue is taken up with ice cold water and dilute hydrochloric acid. The mixture is then extracted with ether to remove neutral impurities. The aqueous solution is then made alkaline with sodium hydroxide solution, and basic substances are extracted with ether. The ether is removed from the dried extract by distillation, and the remaining light yellow oil is distilled *in vacuo*; b.p. 165–167°/0.2 mm.; n_D^{20} 1.5308.

Anal. Calc'd for $C_{17}H_{24}N_2O_2$: N, 9.72. Found: N, 9.51.

The yield of the 2-diethylamino-5-phthalimidopentane is 60%. It forms a crystalline picrate which melts at 137–138°.

Preparation of 2-diethylamino-5-aminopentane (XIII). 2-Diethylamino-5-phthalimidopentane (4 g.) is dissolved in concentrated hydrochloric acid (12 cc.). The clear solution is boiled under a reflux condenser for 10 hours. It is then cooled, and the phthalic acid (2.4 g.) which separates is removed. The filtrate is concentrated to dryness under reduced pressure. The residue is the crude dihydrochloride of 2-diethylamino-5-aminopentane. From this dihydrochloride, the free base is recovered by treatment with 50% sodium hydroxide solution and extraction with ether. The ether is removed from the extract by distillation, and the residue is distilled under reduced pressure; b.p. 103–104°/37 mm.; n_D^{20} 1.4478 (1.6 g.). The picrate of this base, when crystallized from alcohol, melts at 138–140°.

Preparation of 2-piperidino-5-phthalimidopentane. 2-Piperidino-5-phthalimidopentane (*cf.* the preparation of 2-diethylamino-5-phthalimidopentane) is prepared by treating 2-bromo-5-phthalimidopentane with piperidine. The "phthalimido compound" is sufficiently purified if it is heated at 100° and 2 mm. for four hours to remove all volatile impurities. It is a light orange colored oil. The yield is 65%.

2-Piperidino-5-aminopentane is prepared by hydrolysis of the "phthalimido compound" just described; b.p. 90–92°/7 mm.; n_D^{20} 1.4765. The picrate, when recrystallized from methanol, melts at 147–148.5°.

Preparation of 1-diethylamino-3-aminopentane. In the course of establishing the structure of the compound (XIII), obtained by the reaction between 1-diethylamino-4-chloropentane and potassium phthalimide, the possible formation of the diamine $(C_2H_5)_2NCH_2CH_2\underset{\displaystyle NH_2}{\underset{|}{C}}HCH_2CH_3$ was taken into account. This compound was prepared by the following series of reactions. Condensation of β-chloropropionyl chloride with zinc diethyl to give β-chlorodiethyl ketone; treatment of this latter compound with diethylamine to give the β-diethylaminodiethyl ketone; hydrogenation of the oxime of this ketone in the presence of platinum oxide to give 1-diethylamino-3-aminopentane (b.p. 104°/37 mm.; n_D^{20} 1.4430). The picrate of this diamine melts at 155.5–156.5°.

Fourneau (10) mentions a compound of the plasmoquine type which contains the above diamine as a side chain; but he gives no data for the preparation of the diamine. The plasmoquine compound was probably prepared in the usual way from an aminoquinoline and 1-diethylamino-3-chloropentane.

SUMMARY

1. A method for the conversion of quaternary pyrrolidinium compounds to primary-tertiary open-chain diamines has been developed.

2. Alkali phthalimides, when heated with quaternary pyrrolidinium compounds in xylene at 150–160°, rupture the ring and yield the corresponding N-dialkylamine-4-phthalimidopentanes.

3. Alkali succinimides react like the alkali phthalimides.

4. Sodium phenylacetylene and sodium amide with quaternary pyrrolidinium compounds, when heated at 135° in xylene, yield products usually formed in the Hofmann degradation.

5. Quaternary salts derived from pyridine and piperidine, when heated with potassium phthalimide at 150–165° in xylene, yield pyridine, or N-alkyl piperidine, respectively, and an alkylated phthalimide.

6. The Grignard reagents formed from allyl chloride, or substituted allyl chlorides, are more useful synthetic reagents than the Grignard reagents formed from the corresponding allyl bromides, the reagents recommended by other investigators.

7. The preparation and properties of a large number of new unsaturated tertiary amines and unsaturated alcohols are described.

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