REACTION OF 2-ALKYLTETRAHYDROPYRANS
WITH ANILINE OVER ALUMINA

THE VAPOUR-PHASE REACTION
OF
2-ALKYLTETRAHYDROPYRANS WITH ANILINE
OVER ALUMINA

by

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A Thesis
Submitted to the Faculty of Arts and Science
in Partial Fulfilment of the Requirements
for the Degree
Master of Science

McMaster University
October 1952

MASTER OF SCIENCE (1952)
(Chemistry)

McMASTER UNIVERSITY
Hamilton, Ontario

TITLE: The Vapour-Phase Reaction of 2-Alkyltetrahydropyrans with Aniline over Alumina.

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NUMBER OF PAGES: Forty-eight

SCOPE AND CONTENTS: The vapour-phase reaction of 2-methyltetrahydropyran and 2-ethyltetrahydropyran with aniline over an activated alumina catalyst has been studied. The product, in each case, consisted of a mixture of an N-arylpiperidine, an N-arylpyrrolidine formed by ring contraction, and two N-alkenylanilines formed by ring opening. The structures of the nitrogen heterocyclic compounds were established by independent syntheses involving the reaction of the appropriate dibromoalkane with aniline. The N-alkenylanilines were characterized by hydrogenation to known N-alkylanilines and by identification of the ozonolysis products.

ACKNOWLEDGEMENT

The author wishes to express his sincere appreciation to Professor A. N. Bourns whose guidance and assistance proved invaluable to the outcome of this problem.

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INTRODUCTION

Statement of the Problem

Recently, a study has been made in this laboratory of the vapour-phase reaction of tetrahydropyran with aniline and the toluidines over an activated alumina catalyst. Under optimum conditions of temperature and feed rate, yields of 1-arylpiperidines in excess of ninety percent were obtained from tetrahydropyran and aniline, m-toluidine, and p-toluidine. The cyclic ether and o-toluidine gave a somewhat lower yield (66 percent), which may be attributed to the steric effect of the ortho methyl group.

The present investigation extends this study to include the reactions of 2-methyltetrahydropyran and 2-ethyltetrahydropyran with aniline using the conditions found optimum for the parent compound. The product of each reaction, unlike that obtained from tetrahydropyran, distilled over a wide temperature range, and its components could only be separated by careful fractionation. Three narrow boiling fractions were isolated in each case. The structures of the compounds contained in these fractions were established by independent syntheses, degradation, and conversion to known compounds.

Historical

During the past sixteen years, a number of papers have been published dealing with the conversion of oxygen heterocyclic compounds to their corresponding nitrogen analogs by a vapour-phase reaction with ammonia and with amines over an activated alumina catalyst. This unusual reaction was discovered by Yu. K. Yur'ev in 1936 (1) when he observed that pyrrole is formed in a yield of thirty percent when furan and ammonia are passed over activated alumina at 400°C. Yur'ev then extended his investigation to include a study of the reactions of furan, tetrahydrofuran, and their homologs with several aliphatic and aromatic primary amines. He has also investigated the reaction of tetrahydropyran with ammonia and ethylamine. Recently, in our laboratory, this method has been applied with considerable success to the conversion of tetrahydropyran to 1-arylpiperidines.

In addition to the above, Yur'ev has studied other conversions of heterocyclic compounds. The most important of these has been the conversion of oxygen heterocycles to their sulfur analogs by reaction with hydrogen sulfide over alumina. The present review, however, presents only the work of Yur'ev and others on the conversion of oxygen to nitrogen heterocycles by the vapour-phase catalytic method.

Furan and Homologs

Table I lists the results of the reactions of furan and 2-methylfuran with ammonia, aliphatic and aromatic amines. It is to be noted that temperatures of 400°C. and above were used in all cases. In general, yields were lower than thirty percent with furan, and dropped to as low as ten percent when the reaction was applied to 2-methylfuran.

Tetrahydrofuran and Homologs

Higher yields were reported when the reaction was extended to tetrahydrofuran and its homologs. This is to be expected since conjugation of the double bonds of furan with the unshared pair of electrons on the oxygen atom will tend to decrease the ease of carbon-oxygen bond cleavage in this compound. The results of these studies are given in Table II. It may be noted again that temperatures of 400°C. and above were employed and also that yields decreased with methyl substitution on the two position of the ring.

Tetrahydropyran

The results of Yur'ev's work on the reaction of tetrahydropyran with ammonia and ethylamine appear in Table III. A comparison of Table II and Table III shows that slightly lower yields were obtained from tetrahydropyran than from the five membered cyclic compound, tetrahydrofuran.

In 1949, a study was initiated in this laboratory of the reaction of tetrahydropyran and aniline over Alcoa Activated Alumina catalyst (2). The first experiment was carried out using the reaction conditions reported by Yur'ev in his study of the reaction of tetrahydrofuran with this amine. The desired product, 1-phenylpiperidine, was obtained in 58.5 percent yield, which compared favourably with the yield of 1-phenylpyrrolidine obtained by Yur'ev in the reaction with tetrahydrofuran. It was observed, however, that in spite of the low yield of the piperidine compound, no unchanged cyclic ether was present in the reaction product. Furthermore, a considerable amount of low-boiling material as well as resins was found. A careful study of the influence of temperature and other variables on the course of the reaction was then made. Under the optimum conditions of 300-325°C., a ratio of two moles of aniline to one mole of cyclic ether, and a feed rate of thirty milliliters of mixed reactants per hour per one hundred milliliters of catalyst, yields of 1-phenylpiperidine in excess of ninety percent were obtained. Under similar conditions, tetrahydrofuran was converted to 1-phenylpyrrolidine in comparable yields (Table IV). From this it was concluded that Yur'ev, in his investigation of the reaction of tetrahydrofuran, either failed to determine the influence of temperature on the reaction, or had at his disposal a catalyst of lower activity than used in this investigation.

The study was then extended to the reaction of tetrahydropyran with the toluidines. Tolylpiperidines were obtained in over ninety percent yield from m- and p-toluidine and in sixty-six percent from the ortho isomer.

The results of the investigation of the reaction of tetrahydropyran with primary aromatic amines are reported in Table IV.

TABLE I

THE REACTION OF FURAN AND ITS HOMOLOGS WITH AMMONIA AND AMINES OVER ACTIVATED ALUMINA

Furan Compound	Nitrogen Compound	Temperature Degrees C.	Product (Pyrrole Compound)	% Yield	Reference
Furan	Ammonia	450	Pyrrole	30	1
	Ammonia	400	Pyrrole, indole, pyrrocaline, carbazole, etc.	30	3
	Methylamine	400-440	1-Methylpyrrole	24.5	4
	Ethylamine	400-440	1-Ethylpyrrole	27	4
	Amylamine	465-470	1-Amylpyrrole	14	5
	Aniline	465	1-Phenylpyrrole	24	6
	o-Toluidine	465	1-*o*-Tolylpyrrole	40.6	6
	p-Toluidine	465	1-*p*-Tolylpyrrole	21	6
	Benzylamine	395-460	1-Benzylpyrrole	3	7
2-Methylfuran	Ammonia	475	2-Methylpyrrole	24	8
	Aniline	475	1-Phenyl-2-methylpyrrole	12	9
	o-Toluidine	475	1-*o*-Tolyl-2-methylpyrrole	10	9
	p-Toluidine	475	1-*p*-Tolyl-2-methylpyrrole	10	9
2-Ethylfuran	Ammonia	450	2-Ethylpyrrole	5	5

TABLE II

THE REACTION OF TETRAHYDROFURAN AND ITS HOMOLOGS WITH AMMONIA AND AMINES OVER ACTIVATED ALUMINA

Tetrahydrofuran Compound	Nitrogen Compound	Temperature Degrees C.	Product (Pyrrolidine Compound)	% Yield	Reference
Tetrahydrofuran	Ammonia	400	Pyrrolidine	43	10
	Methylamine	400	1-Methylpyrrolidine	35.5	4
	Ethylamine	400	1-Ethylpyrrolidine	56.5	4
	Allylamine	400	1-Allylpyrrolidine		5
	Propylamine	395-460	1-Propylpyrrolidine	41	7
	Butylamine	395-460	1-Butylpyrrolidine	52	7
	Amylamine	390	1-Amylpyrrolidine	55.5	5
	Diethylamine	400	1-Ethylpyrrolidine	29	11
	Triethylamine	400	1-Ethylpyrrolidine	9	11
	Aniline	400	1-Phenylpyrrolidine	45.5	12
	o-Toluidine	400	1-*o*-Tolylpyrrolidine	43.4	12
	p-Toluidine	400	1-*p*-Tolylpyrrolidine	52.7	12
	Cyclopentylamine	400	1-Cyclopentylpyrrolidine	40	5
	Cyclohexylamine	400	1-Cyclohexylpyrrolidine	62.9	12
	Ethylenediamine	400	1,1'-Ethylenedipyrrolidine	small	5
	m-Phenylenediamine	400	1,1'-*m*-Phenylenedipyrrolidine	small	5
2-Methyltetrahydrofuran	Ammonia	400-440	2-Methylpyrrolidine	27	4
	Methylamine	400-440	1,2-Dimethylpyrrolidine	34.5	4
	Ethylamine	400-440	1-Ethyl-2-methylpyrrolidine	28	4
	Aniline	350-450	1-Phenyl-2-methylpyrrolidine	34	7
	o-Toluidine	350-450	1-*o*-Tolyl-2-methylpyrrolidine	8	7
	p-Toluidine	350-450	1-*p*-Tolyl-2-methylpyrrolidine	26	7

TABLE II (Continued)

Tetrahydrofuran Compound	Nitrogen Compound	Temperature Degrees C.	Product (Pyrrolidine Compound)	% Yield	Reference
2,5-Dimethyl-tetrahydrofuran	Ammonia	395-460	2,5-Dimethylpyrrolidine	17.5	7
	Cyclohexylamine	395-460	1-Cyclohexyl-2,5-dimethylpyrrolidine	10.5	7
	Aniline	395-460	1-Phenyl-2,5-dimethylpyrrolidine	19	7
2-Ethyltetrahydrofuran	Ammonia	400	2-Ethylpyrrolidine	9	5

TABLE III

THE REACTION OF TETRAHYDROPYRAN WITH AMMONIA AND AMINES OVER ACTIVATED ALUMINA

Pyran Compound	Nitrogen Compound	Temperature Degrees C.	Product (Piperidine Compound)	% Yield	Reference
Tetrahydropyran	Ammonia	400-430	Piperidine	20	13
	Ammonia	400	Piperidine (traces of Pyridine)	16	14
	Ethylamine	400-430	1-Ethylpiperidine	17	13

TABLE IV

THE REACTION OF TETRAHYDROFURAN AND TETRAHYDROPYRAN WITH AROMATIC AMINES OVER ACTIVATED ALUMINA

Heterocyclic Compound	Nitrogen Compound	Temperature Degrees C.	Product (Piperidine Compound)	% Yield	Reference
Tetrahydrofuran	Aniline	290	1-Phenylpyrrolidine	88	2
Tetrahydropyran	Aniline	300	1-Phenylpiperidine	92	2
	m-Toluidine	325	1-*m*-Tolylpiperidine	94.3	2
	p-Toluidine	325	1-*p*-Tolylpiperidine	92.5	2
	o-Toluidine	340	1-*o*-Tolylpiperidine	66.3	2

RESULTS AND DISCUSSION

The investigation of the reaction of 2-alkyltetrahydropyrans with aniline was carried out by passing the mixed vapours of the reactants over activated alumina at an elevated temperature. The reaction product was then fractionally distilled, and the separated compounds identified by independent synthesis or by degradation and conversion to compounds of established structure.

In carrying out the vapour-phase catalytic reaction, the reactants, mixed in a ratio of one mole of aniline to two of the 2-alkyltetrahydropyran, were fed at a constant rate into a preheater where both compounds were vapourized. The hot vapour was passed over a catalyst bed of activated alumina, maintained at 300°C., and the reaction product was then condensed. The condensate separated into two layers. The aqueous layer was separated from the organic layer, which was dried and carefully fractionated in a modified Podbielniak type column (15).

The Reaction of 2-Ethyltetrahydropyran and Aniline

The reaction product from 2-ethyltetrahydropyran and aniline was separated by careful fractionation into three distinct fractions, the properties of which are as follows:

	Percent by Weight	B.P. at 8 mm. Degrees C.[a]	n_D^{20}	Picrate M.P. Degrees C.[a]
Fraction I (Compound I)	17	126-127	1.5502	178.2-178.8
Fraction II (Compound II)	26	136-137	1.5518	137.0-137.5
Fraction III (Compound III)	57	145-146	1.5364	

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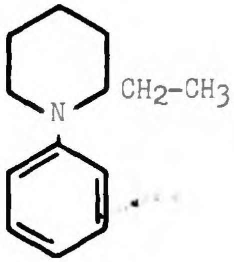
[a] All melting points are corrected; all boiling points are uncorrected.

Elemental analysis indicated that the three compounds were isomeric, the formula of each corresponding to that calculated for a product formed by the elimination of water between one molecule of cyclic ether and one of aniline.

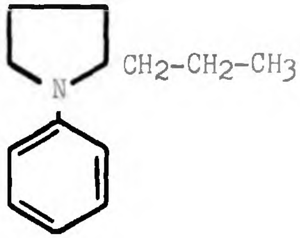
$$C_7H_{14}O + C_6H_5NH_2 \longrightarrow C_{13}H_{19}N + H_2O$$

The usual Hinsberg test with benzenesulfonyl chloride suggested that the three compounds were tertiary amines. Solid picrate derivatives, however, could be formed with Compound I and II only. Substituted benzenesulfonyl chloride derivatives, on the other hand, were formed under special conditions from Compound III, which indicated that this product was either a primary or secondary amine. The fact that these derivatives could not be recrystallized to a constant melting point, however, suggested the fraction which we have called Compound III was actually a mixture of two or more components.

Structures A and B were considered to be the most probable for the two tertiary amines, Compounds I and II.

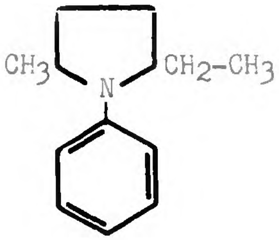


A



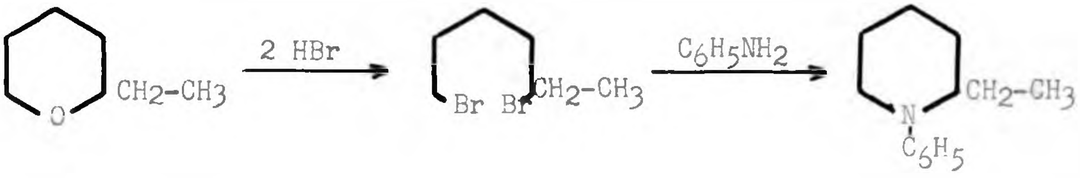
B

Structure A is that of the expected product. Structure B contains a stable five-membered ring which can arise through a rearrangement involving the secondary carbon of the ether linkage. This rearrangement was considered more likely to occur than a rearrangement at the primary carbon, which would result in a product of structure C (16).

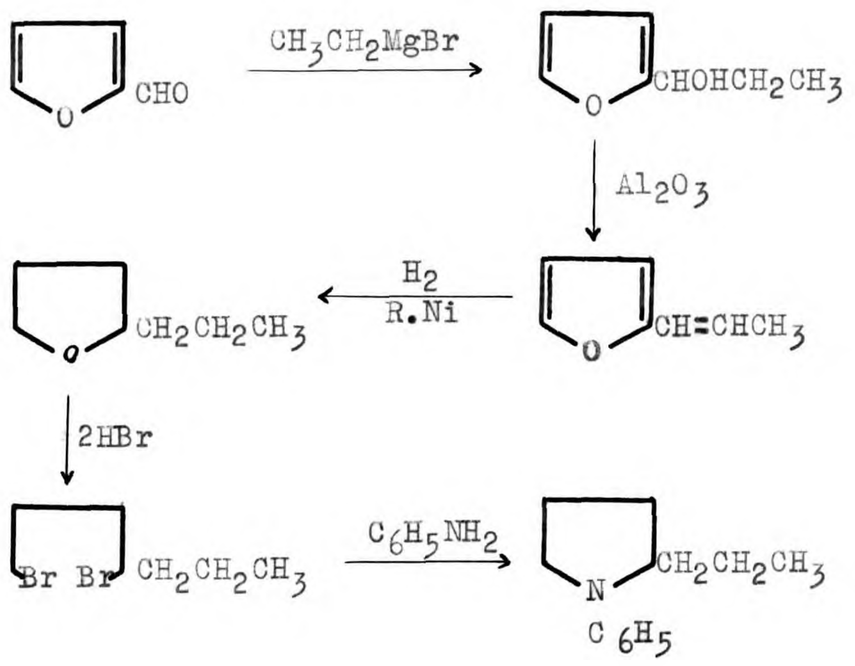


C

An independent synthesis of a compound having the structure A was then undertaken according to the following sequence of reactions:



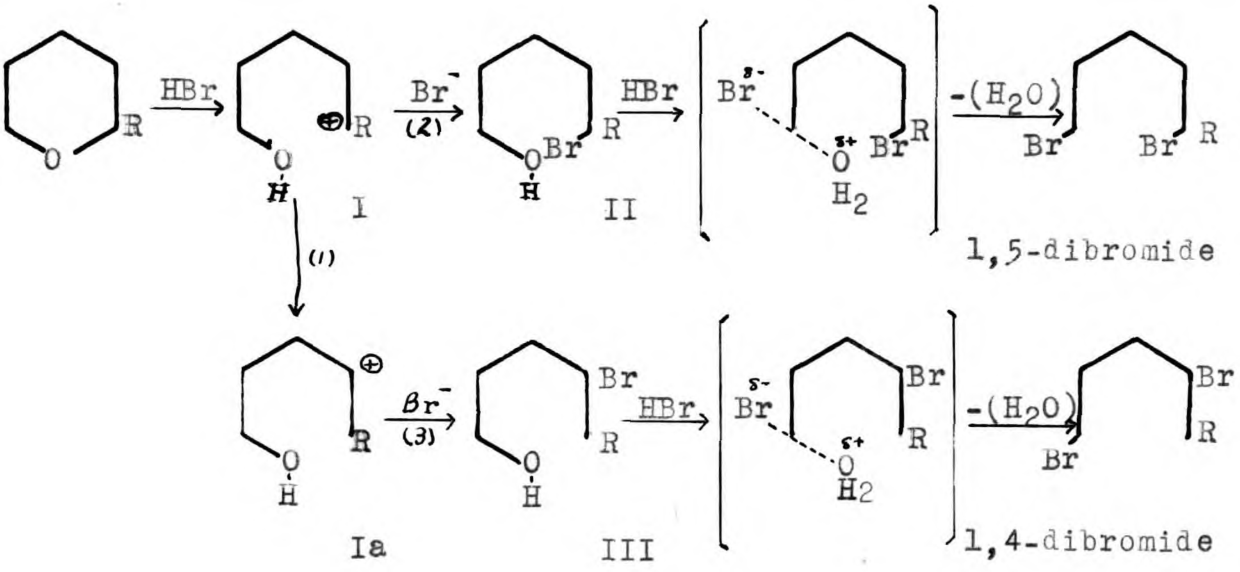
2-Ethyltetrahydropyran was treated with hydrogen bromide to give a dibromide product of narrow boiling range and constant refractive index. This was allowed to react with aniline, and the reaction mixture was then fractionated to yield a product seventy percent of which was shown to be identical with Compound I from a "mixed melting-point" determination of their picrates. The remaining thirty percent was a higher boiling compound which was shown to be identical with Compound II by the same method. Since a compound having the structure A was the expected product, it was assumed that the compound constituting seventy percent of the total product had this structure. To justify this assumption, however, the following independent synthesis of a compound of structure B was attempted.



Furfural was treated with ethyl magnesium bromide and the product, 1-(2-furyl)-1-propanol, was dehydrated over alumina at 300°C. to give a mixed product of 1-(2-furyl)-1-propene and 1-(2-furyl)-propane. This mixture was hydrogenated over Raney nickel to give 2-propyltetrahydrofuran, which was then converted to the dibromide by the action of anhydrous hydrogen bromide in glacial acetic acid. The subsequent reaction with aniline gave a product, which, on fractionation, was separated into two components. The larger fraction, eighty percent of the total product, was shown to be identical with Compound II, while the remaining twenty percent was found to be identical with Compound I.

In each of these two syntheses, one of the products is the desired product, and the other is a product presumably formed by rearrangement. If there was a greater tendency for the compound having either structure A or B to be formed, it would probably constitute the major reaction product in each case. However, because these two syntheses were performed by essentially the same method, and because the minor product of the first synthesis is the major product of the second synthesis, and vice versa, it must be concluded that in both syntheses, the rearranged product is the minor product and the desired product is the major product. Therefore, Compound I was assigned the structure A and Compound II was assigned the structure B, and they were thus identified as being 1-phenyl-2-ethylpiperidine and 1-phenyl-2-propylpyrrolidine, respectively.

These minor or rearranged products were believed to have originated in the syntheses of the dibromide compounds. A mechanism by which this rearrangement may occur is outlined below. It will be noted that, according to this mechanism, the displacement by bromide ion at the secondary carbon has been interpreted as proceeding via a carbonium ion (S_N1), whereas the displacement at the primary carbon is considered to be bimolecular (S_N2).



Reaction (2) and (3) might be expected to proceed rapidly and at about the same rate. Because of this, it is doubtful if an equilibrium between the two carbonium ions I and Ia has sufficient time to be established. If the hydrogen shift (reaction (1)) is other than instantaneous, the rate of formation of the bromoalcohol III from I must be less than the rate of formation of II from this carbonium ion. It follows, therefore, that the rearranged product, in this case the 1,4-dibromide, will be formed at a slower rate that the product of direct displacement, here the 1,5-dibromide. As reported above, this has been found to be the case.

Compound III (Fraction III), as mentioned earlier, was different from Compounds I and II in that it did not form a solid picrate, but instead, formed substituted benzenesulfonamide derivatives, which could not be recrystallized to constant melting point. This suggested that the fraction we have called Compound III was a mixture of secondary amines. Furthermore, since this product was isomeric with Compounds I and II, the seven-carbon chain must contain an ethylenic linkage. This was shown to be the case by hydrogenating it over Raney nickel catalyst. The product of this reaction formed substituted benzenesulfonamide derivatives which were easily recrystallized to a constant melting point and agreed very closely with the literature values of the corresponding derivatives for N-heptylaniline. The boiling point, however, differed greatly from that reported by Emerson and Walters (17) for this product. Therefore, as further proof of the structure of the reduction product, an independent synthesis of N-heptylaniline was carried out.

$$C_6H_{13}CHO + C_6N_5NH_2 \xrightarrow[Pt]{H_2} (C_6H_{13}CH\ NC_6H_5) \longrightarrow C_6H_{13}CH_2NHC_6H_5 + H_2O$$

Aniline was treated with n-heptaldehyde in the presence of sodium acetate, and the resulting anil, without isolation, was immediately hydrogenated over a platinum catalyst to yield N-heptylaniline. Benzenesulfonamide derivatives of this compound and of the corresponding derivative of the reduction product from Compound III gave no depression.

The problem of locating the position of the double bond was solved by ozonolysis followed by identification of the degradation products of the ozonide. It was found that the ozonolysis of Compound III, as the free base, resulted in extensive oxidation, as shown by the fact that the reaction solution turned very dark and the amount of ozone absorbed exceeded the theoretical by several fold. This difficulty was overcome by first benzoylating Compound III with benzoyl chloride in the presence of pyridine, thereby protecting the reactive amino group from oxidative attack. The ozonide, formed by passing a stream of ozone (5 percent) at room temperature into a solution of the benzoylated compound in aldehyde-free propionic acid, was decomposed by hydrogenolysis using palladium on calcium carbonate as the catalyst. The aliphatic aldehydes so formed were swept by means of nitrogen into 2,4-dinitrophenylhydrazine solution. The resulting 2,4-dinitroplenylhydrazones were recrystallized once and chromatographed on a silicic acid super-cel column using a four percent ether in petroleum ether solution as the developing solvent. The less strongly absorbed component of the chromatogram was identified as the 2,4-dinitrophenylhydrazone derivative of propionaldehyde, while the more strongly absorbed component was found to be the corresponding derivative of acetaldehyde. Thus Compound III was shown to be a mixture of N-hept-4-enylaniline and N-hept-5-enylaniline.

The Reaction of 2-Methyltetrahydropyran and Aniline

The dried reaction product of 2-methyltetrahydropyran and aniline was separated into three distinct fractions by careful fractionation in an efficient column. The physical properties of these fractions are listed below.

	Percent by Weight	B.P. at 8 mm. Degrees C.	n_D^{20}	Picrate M.P. Degrees C.
Fraction I (Compound IV)	42	113.0-114.0	1.5528	166.8-167.2
Fraction II (Compound V)	27	125.5-126.5	1.5590	120.6-121.2
Fraction III (Compound VI)	31	132.5	1.5412	

Elemental analysis of the three fractions indicated that they were isomers and corresponded in composition to a compound formed by condensation of the two reactants with the elimination of water.

$$C_7H_{14}O + C_6H_5NH_2 \longrightarrow C_{13}H_{17}N + H_2O$$

As in the case of the products from the 2-ethyl homolog and aniline, the two lower-boiling fractions, Compound IV and V, formed solid picrate derivatives. Compound VI (Fraction III) formed substituted benzenesulfonamide derivatives, but these could not be recrystallized to a constant melting point, a fact which suggested the presence of more than one compound in this fraction,

Since Compounds IV and V were expected to be analogous in structure to I and II, isolated from the reaction of the 2-ethyl homolog, an independent synthesis of 1-phenyl-2-methylpiperidine was attempted. 2-Methyltetrahydropyran was dissolved in glacial acetic acid and the solution treated with anhydrous hydrogen bromide. The resulting dibromide product was purified and then treated with aniline. The product of this reaction, upon careful fractionation, was found to consist of eighty-five percent of a compound shown to be identical with Compound IV, while the compound comprising the remaining fifteen percent of the product was identical with Compound V.

This synthesis was analogous to the independent preparation of 1-phenyl-2-ethylpiperidine in that a major and a minor product resulted. Since it had been established in the latter synthesis that the major component was the expected (unrearranged) compound, it would seem reasonable to assume that this was also the case in the corresponding independent synthesis of the 2-methyl homolog. Thus Compound IV was considered to be 1-phenyl-2-methylpiperidine and Compound V 1-phenyl-2-methylpyrrolidine.

An interesting observation may be made with the aid of Table V, in which a comparison is made of the relative amounts of the tertiary amines formed in the vapour-phase catalytic reaction and in the liquid phase dibromide synthesis.

Comparing the reactions of the two alkyltetrahydropyrans over alumina, it is seen that the substituted pyrrolidine is favoured with respect to the substituted piperidine in the case of the 2-ethyl compound, whereas with the 2-methyl homolog the reverse is true. One might expect, therefore, that in the preparation of the piperidine compounds via the dibromide, there would be less of the pyrrolidine compound formed as a side-reaction product in the 2-methyl synthesis. As is seen from Table V, this was found to be the case.

TABLE V

RELATIVE AMOUNTS OF PIPERIDINE AND PYRROLIDINE PRODUCTS

	Percent of Total Reaction Product	
	Substituted Piperidine	Substituted Pyrrolidine
Vapour-Phase Reaction of 2-Ethyltetrahydropyran	17	26
Vapour-Phase Reaction of 2-Methyltetrahydropyran	42	27
Dibromide Synthesis of 1-Phenyl-2-ethylpiperidine	70	30
Dibromide Synthesis of 1-Phenyl-2-methylpiperidine	85	15

Compound VI was hydrogenated over Raney nickel, and substituted benzenesulfonamide derivatives were formed from the resulting product. The melting points of these derivatives were in excellent agreement with those reported in the literature for the corresponding derivatives of N-hexylaniline. The position of the double bond in the six-carbon side chain of Compound VI was established by ozonolysis of the N-acetyl derivative. From the ozonolysis reaction mixture, after reduction of the ozonides with hydrogen over palladium on calcium carbonate, two aldehydes, acetaldehyde and formaldehyde, were isolated. These were identified by means of suitable derivatives. From these results it has been concluded that the product which we have called Compound VI

(Fraction III) is a mixture of N-hex-4-enylaniline and N-hex-5-enylaniline.

Reaction Mechanism

The results obtained in the reactions of the 2-alkyltetrahydropyrans with aniline are in marked contrast with those obtained from tetrahydropyran itself (2). This is shown clearly in Table VI.

It is of interest to compare the effect of alkyl groups in this vapour-phase reaction with the well known behaviour of primary and secondary alcohols in their reaction with hydrogen halides. Primary alcohols normally may be converted in good yields to the corresponding alkyl halides, no products of rearrangement being formed.

$$CH_3CH_2CH_2CH_2CH_2OH + HX \longrightarrow CH_3CH_2CH_2CH_2CH_2X + H_2O$$

With secondary alcohols, on the other hand, a mixture of products is frequently obtained. Thus, the reaction of 2-pentanol with hydrogen halides (16) gives a mixture of 2-halo- and 3-halopentane.

$$CH_3CH_2CH_2CHOHCH_3 + HX \longrightarrow CH_3CH_2CH_2CHXCH_3 \text{ and } CH_3CH_2CHXCH_2CH_3 + H_2O$$

To account for the two products, Whitmore (16) has suggested that the displacement of the hydroxyl by a halogen proceeds by a carbonium ion mechanism as follows:

TABLE VI

YIELD AND COMPOSITION OF PRODUCTS FROM THE REACTION OF TETRAHYDROPYRAN AND ITS HOMOLOGS WITH ANILINE

Reaction	Total Yield[a] Percent	Percent Composition		
		Piperidine Compound	Pyrrolidine Compound	Alkenyl Aniline
Tetrahydropyran and Aniline	90	1-Phenylpiperidine		
		90	none	none
2-Methyltetrahydropyran and Aniline	76	1-Phenyl-2-methylpiperidine	1-Phenyl-2-ethylpyrrolidine	N-Hex-4-enylaniline N-Hex-5-enylaniline
		42	27	31
2-Ethyltetrahydropyran and Aniline	60	1-Phenyl-2-ethylpiperidine	1-Phenyl-2-propylpyrrolidine	N-Hept-4-enylaniline N-Hept-5-enylaniline
		17	26	57

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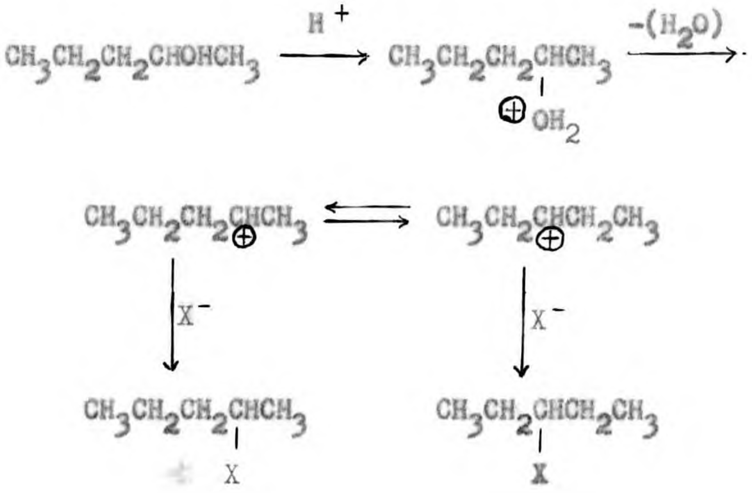
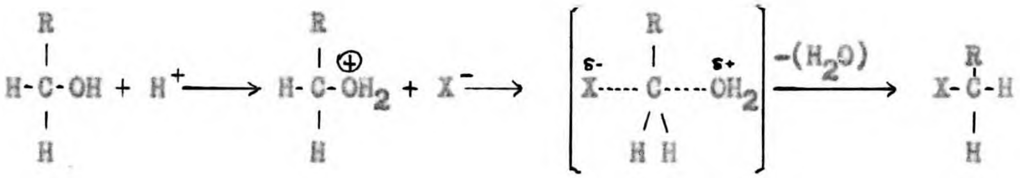
[a] Total yield is based on the amount of cyclic ether charged.



A reaction of this type in which the initial step is the formation of a carbonium ion has been termed by Ingold an S_N1 displacement.

The reaction of primary alcohols with hydrogen halides, on the other hand, is considered to proceed by a bimolecular displacement mechanism, called by Ingold an S_N2 displacement.



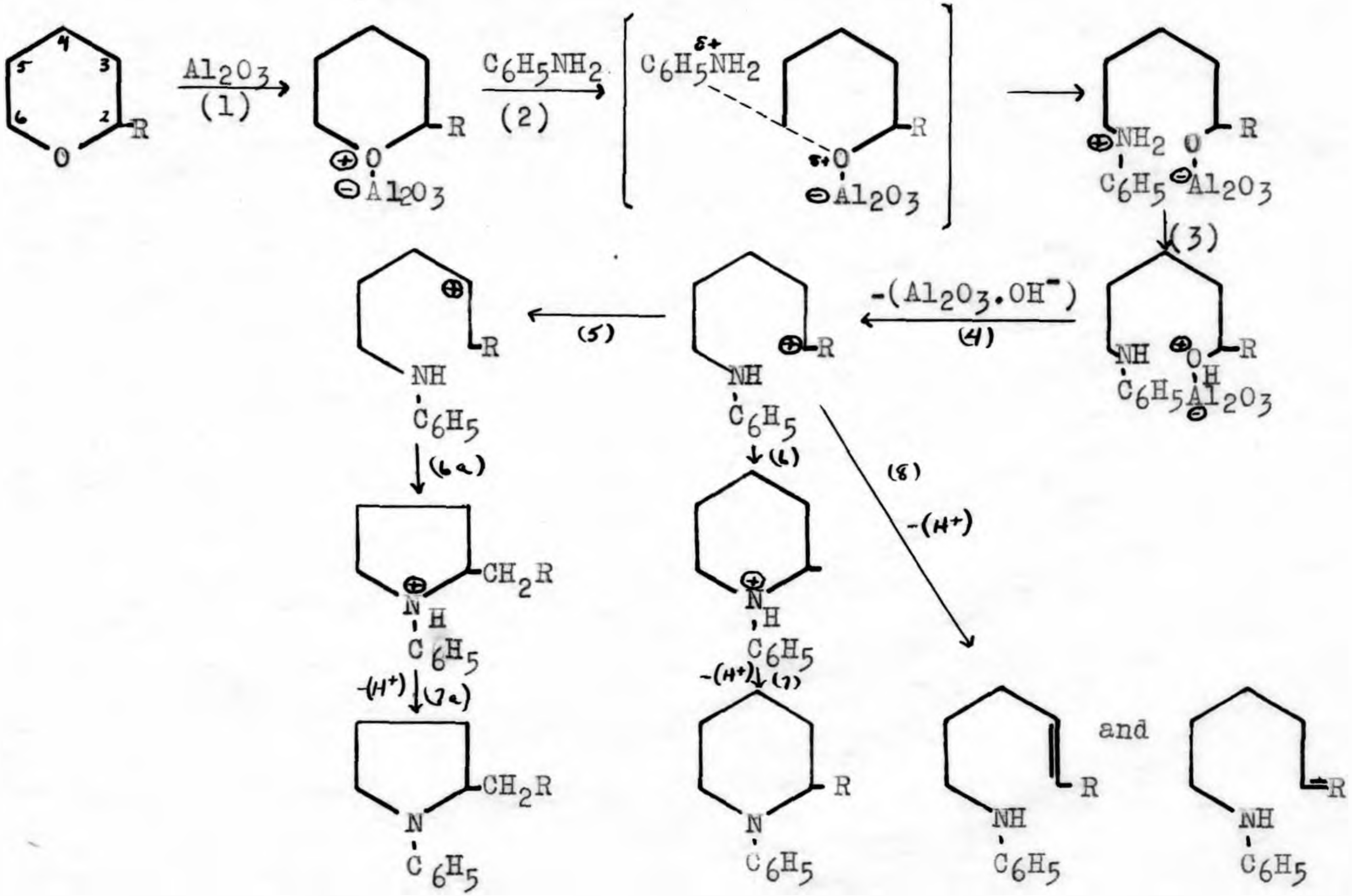
The difference in the mechanism of displacement for the two alcohols is accounted for on the basis of the electron releasing tendency of alkyl groups. The greater the number of alkyl groups on the hydroxylated carbon, the greater will be the energy of repulsion between this carbon and the attacking halogen ion, and therefore the smaller will be the tendency for reaction by the S_N2 mechanism. On the other hand, the accumulation of electron releasing groups on this carbon will stabilize the carbonium ion formed by the S_N1 mechanism, thus favouring displacement by this pathway.

Turning now to the reaction of the 2-alkyltetrahydropyrans with aniline over alumina, it is seen that in forming the reaction products, carbon-oxygen bond cleavage must occur both at a primary and secondary carbon atom. The multiplicity of products formed in this reaction may be accounted for by a mechanism in which the cleavage at the primary carbon atom takes place through a bimolecular displacement (S_N2) with aniline, and the cleavage at the secondary carbon occurs with the formation of a carbonium ion (S_N1). This mechanism is presented on page 23.

It is probable that few, if any, of the intermediates shown in this detailed representation of the reaction mechanism exist as such. They are intended merely to indicate the sequence of events (electron shift, bond cleavage, etc.) which occur during the conversion from reactants to products.

As the alumina catalyst comes in contact with the oxygen atom of the heterocyclic compound, it acts as a Lewis acid by accepting an electron pair from this oxygen atom, to which it imparts a positive charge (Reaction 1). The electrons of the carbon-oxygen bonds are drawn toward the positive oxygen atom, thereby weakening those bonds and leaving the carbon atoms sufficiently positive to present a point of attack for the nucleophilic amino group of the aniline. This attack would be expected to take place on number six rather than on number two carbon atom for two reasons. The alkyl group on carbon number two, because of its electron releasing tendency (-I effect), will tend to neutralize the small positive charge induced on this carbon by the positive oxygen, thereby making the carbon less reactive towards a

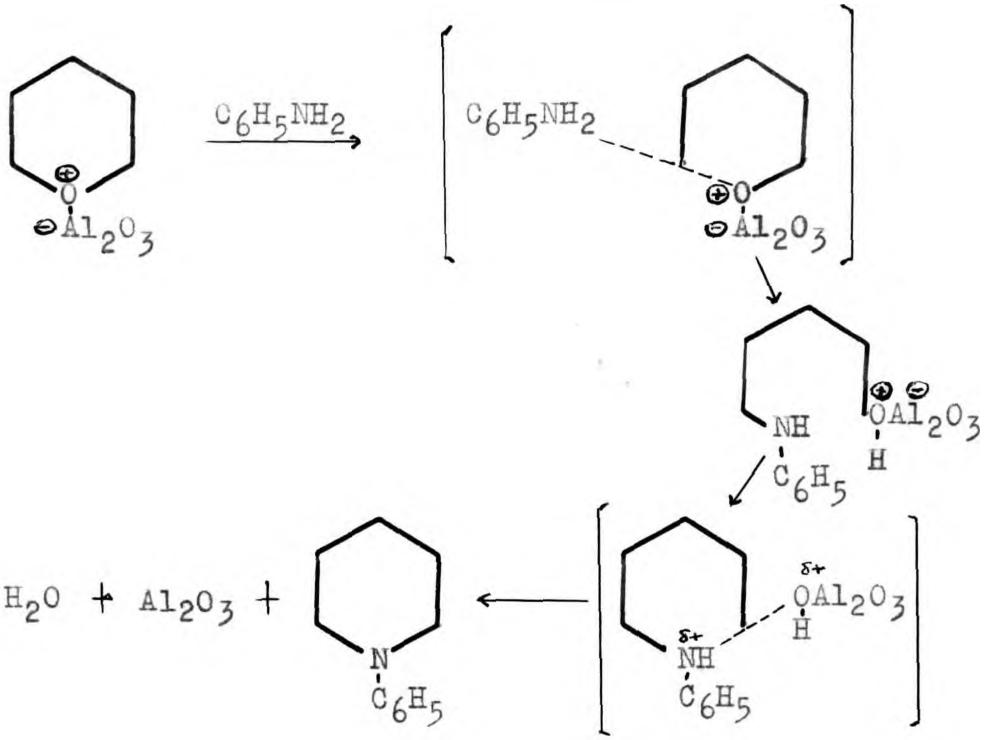
PROPOSED MECHANISM FOR THE REACTION OF 2-ALKYLTETRAHYDROPYRANS AND ANILINE OVER ACTIVATED ALUMINA CATALYST



nucleophilic reagent. Secondly, the alkyl substituent would, by virtue of its size, tend to hinder the approaching aniline molecule.

The nucleophilic amino group of the aniline molecule tends to repel electrons. This repulsion, coupled with the attraction for electrons of the positive oxygen atom, will result in cleavage of the bond between the oxygen and the number six carbon atom (Reaction 2). The shift of a proton from nitrogen to oxygen (Reaction 3) is followed by the cleavage of the carbon-oxygen bond as the organic ion becomes detached from the catalyst (Reaction 4). The resulting carbonium ion may then react in several ways. Ring closure can occur by the formation of a bond between the nucleophilic nitrogen atom and the positively charged carbon atom (Reaction 6). The subsequent loss of a proton (Reaction 7) results in the formation of the substituted piperidine compound. Alternatively a 1,2-shift of a hydrogen atom may occur (Reaction 5) resulting in a second carbonium ion which can then undergo ring closure to give the substituted pyrrolidine (Reactions 6a and 7a). The carbonium ion may stabilize itself in still another way, namely by the loss of a proton from a carbon atom adjacent to the positive center with the subsequent formation of a double bond (Reaction8).

In contrast to the 2-alkyl compounds, the carbon-oxygen bonds in tetrahydropyran involve primary carbon atoms only. Therefore a carbonium ion would not be expected as a reaction intermediate but rather both bond cleavage reactions should proceed by the "bimolecular type" of displacement reaction.



If this is the case, there is no opportunity for either the shift or elimination of hydrogen to give the ring contracted or ring opened products, respectively.

The greater proportion of alkenylanilines in the product of the reaction of 2-ethyltetrahydropyran as compared to that of the 2-methyl homolog may possibly be due to steric factors. It might be expected that the larger the substituent on the positive carbon of the carbonium ion intermediate, the smaller would be the tendency for the ring closure reaction to occur, with the result that the formation of the open chain compound will be favoured.

It is more difficult to account for the relative amounts of the cyclic products in the reaction of aniline with the two tetrahydropyran homologs. From the relative amounts of the piperidine and pyrrolidine compounds formed in the vapour-phase reaction of 2-ethyltetrahydropyran, it would appear that there is a greater inherent tendency for five membered ring formation. This fact is actually not surprising. In the case of the vapour-phase reaction of the 2-methyl homolog, however, the piperidine compound may be favoured for steric reasons, since a methyl group in the carbonium ion leading directly to the six-membered ring should provide considerably less mechanical hindrance to ring closure than the ethyl group in the intermediate ion leading to the five-membered compound.

Referring again to Table VI, a distinct downward trend is apparent in the total yield of reaction product as the size of the 2-alkyl group increases. This may be explained on the basis of the steric hindrance by the alkyl side chain, since intimate contact between the catalyst and the oxygen atom in the heterocyclic compound would probably prove more difficult with a substituent in the two position. Such an effect might be expected to become more apparent as the size of the substituent increases.

EXPERIMENTAL PROCEDURES

Catalysis Experiments

Materials

Aniline:- Baker and Adamson's Purified Grade aniline was distilled from zinc dust and the fraction boiling between 184.0 and 184.2°C. was used in the investigation.

2-Ethyltetrahydropyran:- This compound was prepared from dihydropyran* by the method of Paul (18). Gaseous hydrogen bromide, generated by the action of bromine on dry tetralin (19), was passed into 92.5 g. (1.1 moles) of dihydropyran, immersed in an ice bath, until 81.1 g. (1.0 moles) had been absorbed. The resulting 2-bromotetrahydropyran was diluted with an equal volume of anhydrous ether and the solution added dropwise with stirring to 1.5 moles of a freshly prepared etherial solution of ethyl magnesium bromide maintained at -20°C. The ethyl magnesium bromide solution was prepared by adding dropwise 164 g. (1.5 moles) of ethyl bromide to 37 g. (1.5 moles) of magnesium turnings in in 1000 ml. of anhydrous ether. After the addition of the 2-bromotetrahydropyran solution, the mixture was stirred for an additional thirty minutes and allowed to stand twelve-to-eighteen hours. The product was then treated with crushed ice, the etherial layer separated, the aqueous layer extracted with more ether and the combined etherial extracts dried over anhydrous sodium sulfate. Fractionation yielded 73.1 g. (63.4%)

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* Dihydropyran, kindly supplied by E. I. du Pont de Nemours and Company, (Inc.), was dried over anhydrous calcium sulfate and carefully fractionated. The material, boiling at 85.0°C., n_D^{21} 1.4404 was used in the above synthesis.

of 2-ethyltetrahydropyran, b.p. 126.8-127.1°C., n_D^{20} 1.4262.

2-Methyltetrahydropyran:- This compound was prepared from dihydropyran and methyl iodide following the procedure described for the 2-ethyl homolog. The product, b.p. 101.5-101.8°C. and n_D^{20} 1.4180 was obtained in 76.0% yield.

Catalyst:- The catalyst was Alcoa Activated Alumina (Grade F-1, 4-8 mesh). Fresh catalyst was brought to a condition of maximum activity by passing a stream of air through the catalyst bed heated to 400°C. for seventy-two hours (2). After each run, regeneration was accomplished by passing air through the catalyst bed heated to 400°C. for twenty-four hours.

Catalysis Apparatus

The catalysis furnace consisted of two sections, preheater and catalyst, each with separate heat control. The preheater consisted of a vertical pyrex tube, 30 mm. outside diameter and 18 inches long, packed to a depth of 12 inches with marble chips for heat transfer. The lower end of the preheater tube was connected to the upper end of the catalyst tube by a ground glass joint. The catalyst tube was 30 mm. O.D. and 34 inches long, extending at an angle of 120 degrees with respect to the preheater tube. It was packed with 200 ml. of catalyst which occupied about 15 inches of the central portion of the tube. Heat for the preheater was supplied by a 700 watt, 115 volt Chromel A resistance wire wound on the spiral grooves of an alundum core. Heat for the catalyst zone was supplied by two of these units placed end to end, and wired to permit series or parallel connections. A thin copper tube was fitted inside the refractory heaters to assist in maintaining a uniform temperature throughout the length of the catalyst bed. Both the preheater and the catalyst zones were suitably insulated and the temperatures in each zone were measured by thermocouples moveable along wells concentric with the tubes.

Catalysis Procedure

Aniline and the cyclic ether, mixed in the molar ratio of two to one, were introduced by means of a constant feed device into the upper end of the preheater at a feed rate of 30 ml. of mixed reactants (0.210 moles of 2-alkyltetrahydropyran) per hour per 100 ml. of catalyst. The heat input of this zone was adjusted in order to vapourize and preheat the reactants to 310°C before entering the catalyst zone. The reaction products passing from the catalyst zone were condensed by means of a Friedrich condenser and collected in a suitable receiver. In order to establish equilibrium conditions, a prerun of 40 ml. was always made during which time temperatures and feed rate were given final adjustments. A run usually consisted of 100 ml. of mixed reactants in addition to the prerun.

The product consisted of two layers, the upper organic layer and a lower aqueous layer. The organic layer was salted out, extracted with ether, and dried over sodium hydroxide pellets. The product was then very carefully fractionated in a column described by Elliot (15). The small amount of very low boiling material was separated at atmospheric pressure whereas the aniline and higher boiling reaction products were distilled at 8 mm. pressure.

Reaction of 2-Ethyltetrahydropyran and Aniline

Fractional distillation of the product from the reaction of 2-ethyltetrahydropyran and aniline gave three fractions, the physical properties and relative amounts of which are shown below:

	Percent by Weight	B.P. at 8 mm. Degrees C.	n_D^{20}	Picrate M.P. Degrees C.
Fraction I (Compound I)	17	126-127	1.5502	178.2-178.8
Fraction II (Compound II)	26	136-137	1.5518	137.0-137.5
Fraction III (Compound III)	57	145-146	1.5364	

The figures giving the percent composition of the product are the average of three runs, the deviation being of the order of

The total overall yield, including small midfractions, was 60.0 1%, based on the amount of 2-ethyltetrahydropyran charged.

Anal.* Calcd. for $C_{13}H_{19}N$: C,82.40; H,10.11; N,7.49.

Found Compound I : C,82.70,82.64; H,10.32,10.40; N,7.13,7.18.

Found Compound II : C,82.60,82.70; H,10.39,10.42; N,7.00,6.90.

Found Compound III: C,82.90,82.80; H,10.09,10.08; N,7.13,7.05.

Identification of Compound I - 1-Phenyl-2-ethylpiperidine

Reaction of 2-ethyltetrahydropyran with hydrogen bromide:- This reaction was carried out using the method reported by Wilson (20) for the conversion of tetrahydropyran to 1,5-dibromopentane. 2-Ethyltetrahydropyran, 30.0 g. (0.26 moles) was added slowly to a cold mixture of 340 g. of 48 percent hydrobromic acid and 18.0 ml. of concentrated

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*All analyses were carried out at the Dominion Rubber Research Laboratory, Guelph, Ontario.

sulfuric acid. After refluxing for three hours, the mixture was steam distilled, the distillate extracted with ether, the ether solution washed with sodium carbonate colution, and then dried over anhydrous calcium chloride. Fractionation yielded 44.4 g. (66.3%) of dibromide product, b.p. 112.0-116.0°C. (12 mm.) n_D^{17} 1.5010-1.5025. The formation of the two products in the subsequent reaction with aniline would suggest that the dibromide product consisted of both 1,5-dibromoheptane and 1,4-dibromoheptane with the former predominating (70 percent of the total).

Reaction of aniline with the dibromide product:- The reaction of the dibromide with aniline was carried out following the method reported by Braun (21) for the reaction of 1,5-dibromopentane with aniline and the toluidines. A mixture of 38.5 g. (0.15 moles) of the dibromoheptane product and 62.2 g. (0.68 moles) of aniline was warmed on a steam bath until the reaction turned to a brown crystalline cake. This cake was then dissolved in hydrochloric acid, and the resulting solution treated with sodium hydroxide in order to liberate the product and excess aniline from their hydrobromide salts. The organic layer was extracted with ether and dried over sodium hydroxide pellets. Careful fractionation separated the product into (a) 12.5 g. of 1-phenyl-2-ethylpiperidine, b.p. 125.5-126.0°C. (8 mm.), n_D^{20} 1.5505, picrate m.p. 177.6-178.2°C., and (b) 5.3 g. of 1-phenyl-2-propylpyrrolidine, b.p. 132-136°C. (8 mm.), n_D^{20} 1.5534, picrate m.p. 135.6-136.1°C. The total yield was 63 percent. A mixture of the picrate of (a) and that of Compound I melted at 177.6-179.2°C., and a mixture of the picrates of (b) and Compound II melted at 134.5-137.2°C.

Identification of Compound II - 1-Phenyl-2-propylpyrrolidine

1-(2-Furyl)-1-propanol:- Ethyl magnesium bromide was prepared by adding dropwise 150 g. (1.38 moles) of ethyl bromide in 600 ml. of dry ether to 33 g. (1.38 moles) of magnesium turnings and then refluxing for forty-five minutes. The solution was cooled in an ice bath and 105 g. (1.09 moles) of furfural in 200 ml. of dry ether were added very slowly. After allowing the mixture to stand for twelve-to-eighteen hours, ice and ammonium chloride solution were added, the product was extracted with more ether, and the etherial solution was dried over anhydrous sodium sulfate. The product was vacuum distilled and the material boiling from 74.0-84.0°C. (9.5 mm.) was collected to give 109.3 g. (79.5%) of 1-(2-furyl)-1-propanol.

2-Propyltetrahydrofuran (22) (23):- 1-(2-Furyl)-1-propanol, 72.3 g. (0.57 moles) was passed over activated alumina at 300°C. and a feed rate of 0.43 moles per 100 ml. of catalyst per hour. The reaction product was extracted with ether, dried over sodium hydroxide pellets and fractionated. The product, b.p. 125-130°C., 42.0 g., consisted of 1-(2-furyl)-1-propene together with a small amount of 1-(2-furyl)-propane. This mixture was then subjected to a two-stage hydrogenation* over Raney nickel catalyst in ethanol solution. The first stage of the hydrogenation was carried out at room temperature, whereas the second stage was carried out at 110-115°C. The initial pressure was 1300 lb. per square inch. Following the removal of the catalyst by centri-

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*Hydrogenation was carried out at the Dominion Rubber Research Laboratory, Guelph, Ontario.

fugation, the product was distilled to yield 36.4 g. (82.4%) of 2-propyltetrahydrofuran, b.p. 130-133°C., n_D^{20} 1.4215. Paul (23) reports b.p. 135°C. (773 mm.), n_D^{10} 1.4255 for this compound; Shuikin et al. (24) report b.p. 132-133°C.(756 mm.), n_D^{20} 1.4242.

Reaction of 2-propyltetrahydrofuran with hydrogen bromide:- The method described by Paul (23) was used with minor modifications. A solution of 36.0 g. (0.315 moles) of 2-propyltetrahydrofuran in an equal volume of glacial acetic acid was saturated with anhydrous hydrogen bromide and then heated in a sealed tube at 120°C. for three hours. The product was steam distilled, the distillate extracted with ether, and dried over anhydrous sodium sulfate and phosphorous pentoxide. Careful fractionation yielded 61 g. (75%) of dibromide product, b.p. 108-110°C. (11 mm.), n_D^{20} 1.5010-1.5015.

Reaction of Aniline with the dibromide product:- This reaction was carried out following the procedure already described on page 31. The product from 57.6 g. (0.22 moles) of dibromide and 84.3 g. (0.91 moles) of aniline gave on fractionation two compounds, (a) 6.3 g. of 1-phenyl-2-ethylpiperidine, b.p. 126-129°C. (8 mm.), n_D^{20} 1.5502, picrate m.p. 177.2-177.6°C. and (b) 30.7 g. of 1-phenyl-2-propylpyrrolidine, b.p. 137-138°C. (8 mm.), n_D^{20} 1.5518, picrate m.p. 136.0-136.5°C.* Total yield was 87.5 percent. A mixture of the picrates of (a) and Compound I melted at 177.2-178.2°C., and a mixture of the picrate of (b) and that of Compound II melted at 136.0-136.6°C.

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*A melting point of 142°C. has been reported by Normant (25) for the picrate of 1-phenyl-2-propylpyrrolidine. Our product, although melting six degrees lower, had been crystallized to constant melting point.

Identification of Compound III - N-Heptenylaniline

Reduction of Compound III:- The reduction was accomplished by dissolving 6.4 g. of Compound III in 100 ml. of 95 percent ethanol and hydrogenating in a Parr low pressure hydrogenator at room temperature and a pressure of 50 p.s.i. using approximately 3 g. of Raney nickel catalyst. After separating the catalyst by centrifugation and flashing off the alcohol, the product was distilled *in vacuo* to give 5.1 g. (79%) of N-heptylaniline, b.p. 163.0-169.0°C. (24 mm.), n_D^{20} 1.5186. Emerson and Walters (17) report b.p. 125-130°C. (30 mm.), n_D^{20} 1.5080 for this compound, whereas Hickenbottom (26) reports a b.p. 160-161°C. (21 mm.).

Substituted sulfonamide derivatives were prepared by a method outlined by Hickenbottom (27). One half gram of amine, 0.95 g. of the sulfonyl chloride compound, and 2.5 ml. of pyridine were mixed and allowed to stand at room temperature for eighteen hours. The mixture was then refluxed on a steam bath for two hours, cooled, and poured into 200 ml. of cold water. The solid derivative, which usually formed immediately, was filtered and recrystallized from aqueous alcohol. The following derivatives were so prepared:

p-bromobenzenesulfonamide	m.p.	found	117.0-118.0°C.
		lit.	115°C. (17)
m-nitrobenzenesulfonamide	m.p.	found	96.2-97.2°C.
		lit.	96°C. (26)
p-toluenesulfonamide	m.p.	found	75.2-75.8°C.
		lit.	76°C. (26)

Independent synthesis of N-heptylaniline:- The reductive alkylation procedure of Emerson and Walters (17) was used for the independent synthesis of N-heptylaniline. n-Heptaldehyde, 13.9 g. (0.12 moles), aniline, 6.6 g. (0.071 moles), 1 g. of sodium acetate, and 0.1 g. of platinum catalyst (28) (29) were mixed with 100 ml. of ethanol and the mixture treated with hydrogen in the Parr low pressure hydrogenator at room temperature for thirty-six minutes at a pressure of 58 p.s.i. The catalyst was removed by centrifugation, the alcohol removed by distillation, and the residue vacuum distilled to give a small yield of N-heptylaniline, b.p. 150-170°C. (18 mm.), n_D^{20} 1.5040. The p-bromobenzenesulfonamide derivative, prepared by the method described above, melted at 117.0-118.0°C. A "mixed melting point" with the same derivative of the reduced Compound III gave no depression.

Ozonolysis of trans-N-hex-4-enylaniline:- In order to determine the feasibility of using the ozonolysis reaction for the location of the double bond in Compound III, the method was applied to an unsaturated amine of known structure, trans-N-hex-4-enylaniline. (For synthesis and properties of this compound, see Appendix.) Ozonolysis of this compound as the free base in glacial acetic acid solution resulted in extensive oxidation as shown by the fact that the solution turned very dark and the amount of ozone absorbed exceeded the theoretical by several fold. The unsaturated secondary amine was then converted to its N-benzoyl derivative.(see Appendix). This compound proved quite satisfactory for the ozonolysis reaction, showing no signs of decomposition.

Benzoylation of Compound III:- To a solution of 3.8 g. (0.02 moles) of Compound III in 38 ml. of dry pyridine and 76 ml. of dry benzene was added dropwise 4.8 g. (0.034 moles) of benzoyl chloride, and the solution was maintained at 60-70°C. for thirty additional minutes. The reaction mixture was poured into 700 ml. of water, stirred, and the benzene layer separated. The aqueous layer was extracted with benzene, the combined benzene solutions were washed successively with water, 5% sodium carbonate solution, water again, and finally dried over anhydrous calcium sulfate. Distillation yielded 4.6 g. of a thick, straw-coloured oil, b.p. 163-173°C. (0.3 mm.), 78.4% yield of N-benzoyl-N-heptenylaniline.

Ozonolysis of N-benzoyl-N-heptenylaniline:- A stream of ozone (5%) (30) was passed into a solution of 3.2 g. of N-benzoyl-N-heptenylaniline in 50 ml. of aldehyde-free propionic acid at room temperature and at a rate of 7.5 liters per hour. When the reaction was com plete, that is, when the solution of potassium iodide, which was connected in series behind the reaction solution, turned brown, the ozonide was decomposed by hydrogenolysis for ten hours over palladium on calcium carbonate catalyst (31) at a pressure of 63 p.s.i. and at room temperature. Following the removal of the catalyst by centrifugation, the carbonyl compounds, formed by ozonolysis, were swept into alcohol cooled to dry ice temperature, by bubbling nitrogen through the gradually heated reaction mixture. The progress of the removal of these compounds was followed by periodically passing the nitrogen gas briefly into 2,4-dinitrophenylhydrazine test solutions.* The alcohol solutions of the carbonyl compounds were treated with 2,4-dinitrophenylhydrazine

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* 2,4-Dinitrophenylhydrazine solution made with sulfuric acid was superior for detection purposes, whereas that made with hydrochloric acid was superior for identification purposes.

reagent and the resulting 2,4-dinitrophenylhydrazones were recrystallized once from ethanol and separated chromatographically (32) as follows. The mixed hydrazones (20 mg.) were dissolved in a minimum of a one part benzene to two parts petroleum ether (boiling range 30-60°C.) solution and placed on a column, 25 mm. in diameter and 320 mm. long, composed of two parts of silicic acid and one part Supercel. The chromatogram was developed using a four percent ether in petroleum ether (boiling range 30-60°C.) solution. The mixture separated into two bands which were eluted with developing solvent, and collected separately. After the solvent was removed under reduced pressure, the residues from corresponding bands obtained in several similar operations were mixed and rechromatographed. This time the columns were extruded, and the major bands in each case dissolved in alcohol. The less strongly absorbed derivative, after recrystallizing from alcohol, melted at 153.3-154.8°C., and exhibited no depression of the melting point when mixed with the corresponding derivative of propionaldehyde. The more strongly absorbed compound melted at 166.0-167.0°C. after recrystallizations from ethanol. A "mixed melting point" with the corresponding derivative of acetaldehyde gave no depression.

Reaction of 2-Methyltetrahydropyran and Aniline

Fractional distillation of the product from the reaction of 2-methyltetrahydropyran and aniline gave three fractions, the physical properties and relative amounts of which are shown in the following table.

	Percent by Weight	B.P. at 8 mm. Degrees C.	n_D^{20}	Picrate M.P. Degrees C.
Fraction I (Compound IV)	42	113.0-114.0	1.5528	166.8-167.2
Fraction II (Compound V)	27	125.5-126.5	1.5590	120.6-121.2
Fraction III (Compound VI)	31	132.5	1.5412	

The figures giving the percent composition of the product are the results of a single run, the combined yield, including small midfractions, being 75.8 percent, based on the 2-methyltetrahydropyran charged.

Anal. Calcd. for $C_{12}H_{17}N$: C,82.23; H,9.78; N,7.99.

Found Compound IV: C,81.83,81.61; H,9.80,9.63; N,7.96,8.05.

Found Compound V : C,81.74,81.92; H,9.56,9.66; N,7.74,8.04.

Found Compound VI: C,81.97,81.83; H,9.66,9.57; N,8.04,7.79.

Identification of Compound IV and V - 1-Phenyl-2-methylpiperidine and 1-Phenyl-2-ethylpyrrolidine

Reaction of 2-methyltetrahydropyran and hydrogen bromide:- 2-Methyltetrahydropyran, 18.0 g. (0.18 moles), was dissolved in 21.4 ml. of glacial acetic acid and treated with anhydrous hydrogen bromide at 120°C. following the procedure described above for the reaction of 2-propyltetrahydrofuran with hydrogen bromide. A dibromide product of 35.7 g. was obtained, 82% yield, b.p. 100.0-102.3°C. (12 mm.), $n_D^{13.5}$ 1.5077. The formation of two compounds in the subsequent reaction with aniline indicated that the dibromide product consisted of 1,5-dibromohexane and 1,4-dibromohexane with the former greatly predominating (85 percent of the total).

Reaction of aniline with the dibromide product:- The reaction with aniline was carried out in the manner already described (p. 31).

From 34.5 g. of the dibromide was obtained 19.3 g. of a product which by very careful fractionation was separated into two compounds, (a) 16.9 g. of 1-phenyl-2-methylpiperidine b.p. 110.8-113.0°C. (8 mm.), n_D^{13} 1.5560, picrate m.p. 167.4-168.4°C., and (b) 2.4 g. of 1-phenyl-2-ethylpyrrolidine, b.p. 117.5-118.5°C. (8 mm.), $n_D^{14.0}$ 1.5631, picrate m.p. 118.0-119.0°C. The total yield was 91.8%. A mixture of the picrate of (a) and that of Compound IV melted at 167.4-168.4°C., and a mixture of the picrates of (b) and Compound V melted at 118.0-119.5°C.

Identification of Compound VI - N-Hexenylaniline

Reduction to N-hexylaniline:- A sample of Compound III was dissolved in 100 ml. of ethanol and hydrogenated in the Parr apparatus at room temperature and a pressure of 42.7 p.s.i. over 3 g. of Raney nickel catalyst. After the catalyst had been separated and the alcohol distilled off, the product was distilled under vacuum to give N-hexylaniline, b.p. 163-165°C., (30 mm.), n_D^{20} 1.5230. Hickenbottom (26) reports a boiling point of 158°C. (28 mm.) for this compound.

Substituted sulfonamide derivatives were prepared in the manner already described (p. 34).

m-nitrobenzenesulfonamide	m.p.	found	79.6-80.2°C.
		lit.	79-80°C. (26)
p-toluenesulfonamide	m.p.	found	67.0-68.0°C.
		lit.	67-68°C. (26)
p-bromobenzenesulfonamide	m.p.	found	96.2-97.2°C.

Acetylation of Compound VI:- A solution of 4.5 g. of Compound VI dissolved in 10.6 ml. of acetic anhydride and 70.8 ml. of pyridine was refluxed for one and one half hours. When cool, 360 ml. of 2 percent sulfuric acid solution were added, the product was extracted with ether, and the etherial solution dried over potassium hydroxide pellets. After removal of the ether, the product was distilled <u>in vacuo</u> to yield 4.75 g. (85%) of N-acetyl-N-hexenylaniline, b.p. 115-120°C. (0.5 mm.), n_D^{21} 1.5223.

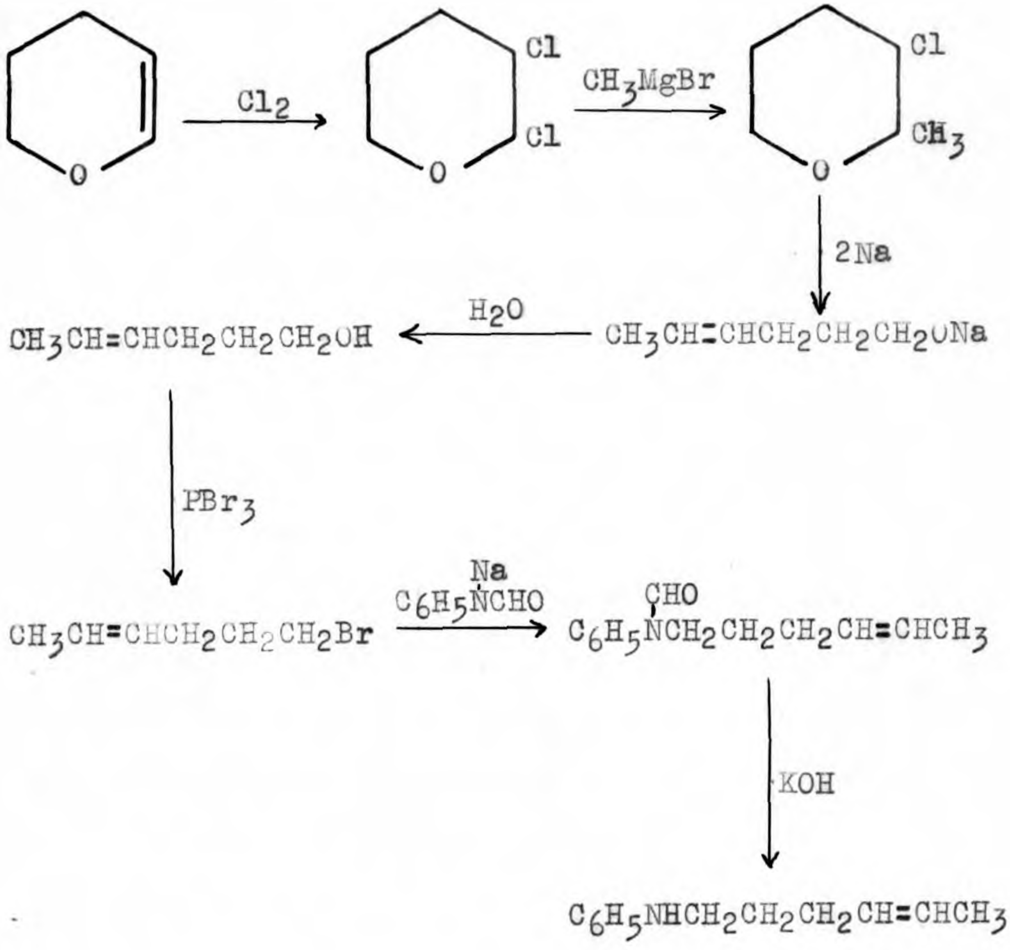
<u>Ozonolysis of N-acetyl-N-hexenylaniline</u>:- A stream of ozone (5%) (30) was passed into a solution of 2g. of N-acetyl-N-heptenylaniline in 50 ml. of purified glacial acetic acid at room temperature and at a rate of 3.6 liters per hour. When the reaction was complete, i.e. when the potassium iodide solution turned brown, the ozonide was decomposed by hydrogenolysis for 31 hours over palladium on calcium carbonate catalyst (31) at a pressure of 47.2 p.s.i. and at room temperature. After the catalyst had been removed by centrifugation, nitrogen gas was bubbled through the solution, heated gradually from 12 to 91°C., and led successively into 2,4-dinitrophenylhydrazine solution and into two test tubes, immersed in a dry-ice and acetone bath, containing ethanol. The precipitate which formed in the 2,4-dinitrophenylhydrazine solution was recrystallized from ethanol, and melted at 164.2-165.8°C. A mixture of this derivative and the 2,4-dinitrophenylhydrazone derivative of acetaldehyde melted at 165.0-166.6°C. From the first alcohol solution, a p-nitrophenylhydrazone derivative was prepared, and melted at 127.2-128.0°C. after recrystallization from ethanol. When mixed with a p-nitrophenylhydrazone derivative of acetaldehyde, a melting point range of 127.2-129.2°C. was observed. The second alcohol solution, which contained that portion of the carbonyl product removed from the reaction mixture at the higher temperature, was treated with methone

and the resulting derivative recrystallized from ethanol. It exhibited a melting point of 190.8-191.8°C. and a "mixed melting point" with a dimethone derivative of formaldehyde of 190.8-192.0°C.

APPENDIX

Synthesis of trans-N-Hex-4-enylaniline

The following sequence of reactions was used in the synthesis of trans-N-hex-4-enylaniline:



L. Crombie and S. H. Harper (33) had previously prepared the intermediate, trans-4-hexenol, by this method, and had established its configuration. In the conversion of this compound to the corresponding bromide and its subsequent reaction with sodium formanilide, it has been assumed that the trans configuration has been retained. This is supported by the fact that the derivatives of trans-N-hex-4-enylaniline showed no change in melting point after one recrystallization.

Experimental Procedure

trans-4-Hexenol:- The method outlined by Crombie and Harper (33) was used to prepare this compound. Chlorine was passed into a solution of 84.0 g. (1.0 moles) of dihydropyran and 200 ml. of dry ether, maintained at 0-5°C., until the solution turned a yellow-green colour. More dihydropyran was then added until the solution was again just colourless. Meanwhile, 1.5 moles of methyl magnesium bromide was prepared by slowly adding 150.0 g. (1.58 moles) of methyl bromide, dissolved in 300 ml. of anhydrous ether, to 37.0 g. (1.5 moles) of magnesium turnings, and refluxing the reaction mixture for ten minutes. The etherial solution of the chlorinated compound was then added to the Grignard solution at a rate such as to maintain a temperature of 5-15°C. when the reaction vessel was immersed in an acetone and dry-ice bath. After the addition of the 2,3-dichlorotetrahydropyran, the mixture was stirred for an additional thirty minutes and allowed to stand twelve-to-eighteen hours. The reaction mixture was then treated with crushed ice and ammonium chloride solution, the etherial layer was separated, the aqueous layer extracted with more ether, and the combined etherial solutions dried over anhydrous calcium carbonate. The product, 2-methyl-3-chlorotetrahydropyran, was distilled from a modified Claisen flask and collected over the range 120-173°C., yield

105.5 g. (78%), n_D^{20} 1,4600.

A few drops of this compound were then added to sodium sand (34) covered with dry ether, and the mixture stirred until a reaction commenced, as shown by the appearance of an indigo blue colour and refluxing of the ether. The remainder of the 2-methyl-3-chlorotetrahydropyran was then slowly added with stirring, after which the mixture was further stirred for two hours at room temperature. Ice and water were then added very cautiously until the thick blue suspension dissolved to form two yellow layers. The lower aqueous layer was separated and extracted with ether three times and the combined ether solutions were dried over anhydrous sodium sulfate. A vacuum distillation of the product gave 59.9 g. (75.3%) of trans-4-hexenol, b.p. 70-73°C. (16.5 mm.), n_D^{20} 1.4406. Crombie and Harper (33) reported b.p. 86.5°C. (15 mm.), n_D^{20} 1.4403 for this compound.

trans-4-Hexenylbromide:- The method reported by Crombie and Harper (33) for preparing 4-heptenylbromides from 4-heptenols was used. Phosphorous tribromide, 33 g. (0.12 moles), was slowly added to a well stirred solution of 30 g. (0.30 moles) of trans-4-hexenol and 6.5 g. of pyridine immersed in an ice bath. The mixture was then stirred for one and one quarter hours at 0°C., and one and three quarter hours at room temperature. The crude bromide was distilled directly from the reaction flask *in vacuo* until frothing of the orange residue was observed. The distillate was then dissolved in 75 ml. of petroleum ether (boiling range 30-60°C.) and washed twice with ten percent hydrochloric acid, once with ten percent sodium hydroxide, and once with water before being dried over anhydrous sodium sulfate. When the product was distilled, a white precipitate appeared. This was separated by centrifugation, the bromide was again dissolved in petroleum ether, washed successively with ten percent hydrochloric acid solution, ten percent sodium hydroxide solution, water, and dried over anhydrous sodium sulfate. Distillation yielded 27.7 g. (56.7%) of product free from precipitate, b.p. 43-46°C. (12 mm.), n_D^{20} 1.4692.

Anal. Calcd. for $C_6H_{11}Br$: C,44.11; H,6.79; Br,49.10.

Found: C,44.24,44.19; H,7.09,6.85; Br,49.04,49.21.

trans-N-Hex-4-enylaniline:- The method developed by Claisen et al. (35) for the preparation of alkenylanilines was used with modifications for the synthesis of trans-N-hex-4-enylaniline. A solution of 10 g. (0.083 moles) of formanilide, dissolved in 40 ml. of dry toluene, was added to 1.8 g. (0.078 moles) of sodium sand, and the mixture was refluxed with stirring for one and one quarter hours. When the reaction mixture had cooled to room temperature, 13 g. (0.080 moles) of trans-4-hexenylbromide were slowly added with stirring. This was followed by a thirteen and one half hour period of refluxing and stirring. After this reaction mixture had cooled, an aqueous solution of sodium bromide was added, the toluene layer decanted, and the aqueous layer extracted three times with petroleum ether (boiling range 30-60°C.). The toluene layer and the petroleum ether solutions were combined and washed six times with dilute alkali, twice with dilute formic acid, and dried over anhydrous sodium sulfate. A vacuum distillation yielded 11.7 g. (73.5%) of trans-N-hex-4-enylformanilide, b.p. 160-164°C. (8 mm.) n_D^{20} 1.5295.

The entire product was refluxed with concentrated methanolic potassium hydroxide solution for one and three quarter hours, cooled, extracted with benzene, and the benzene solution dried over potassium hydroxide pellets. A vacuum distillation of the reaction product gave 7.4 g. (74%) of trans-N-hex-4-enylaniline, b.p. 137-140°C. (9 mm.), n_D^{22} 1.5368.

Anal.Calcd. for $C_{12}H_{17}N$: C,82.23; H,9.78; N,7.99.

Found: C,81.92,81.74; H,9.60,9.64; N,8.03,8.14.

The following derivatives of trans-N-hex-4-enylaniline were prepared using the procedure described on page 34.

m-nitrobenzenesulfonamide derivative	m.p. 89.5-90.0°C.
p-bromobenzenesulfonamide derivative	m.p. 80.8-81.3°C.
p-toluenesulfonamide derivative	m.p. 59.5-60.0°C.

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