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THE REACTION OF TETRAHYDROPYRAN WITH PRIMARY AROMATIC AMINES OVER ACTIVATED ALUMINA[1]

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ABSTRACT

The vapor-phase reaction over activated alumina of tetrahydropyran with aniline and the toluidines has been investigated. Under optimum conditions, N-arylpiperidines were obtained in over 90% yield from aniline, *m*-toluidine, and *p*-toluidine. The cyclic ether and *o*-toluidine gave N-*o*-tolylpiperidine in a maximum yield of 66%. N-Phenylpyrrolidine was obtained in 88% yield from tetrahydrofuran and aniline as compared to 45.5% previously reported by Yur'ev.

During the past 15 years, Yur'ev and his coworkers have carried out an extensive investigation of the reaction of oxygen heterocyclic compounds, in particular, furan, tetrahydrofuran, and their methyl homologues, with ammonia and with amines over activated alumina. It was found, in general, that furan could be converted to pyrrole and to N-alkyl- and N-arylpyrroles in 20-30% yield, while tetrahydrofuran gave the corresponding pyrrolidines in 40-60% yield. Reaction temperatures, for the most part, were 400°C. or higher. Under these conditions, tetrahydrofuran with aniline, *o*- and *p*-toluidine gave, respectively, N-phenylpyrrolidine, N-*o*-tolylpyrrolidine, and N-*p*-tolylpyrrolidine in 45.5, 43.4, and 52.7% yield (4). Yur'ev (5) has also studied the reaction of tetrahydropyran with ammonia and ethylamine, obtaining piperidine and N-ethylpiperidine in 20 and 17% yield, respectively.

The investigation reported in this paper has been concerned primarily with a study of the reaction of tetrahydropyran with aniline and the three toluidines over Alcoa Activated Alumina. It was prompted by the recent availability of tetrahydropyran as a commercial chemical and by the excellent results of Evans and Bourns (1) in their recent investigation of the reaction of aniline with dimethyl ether over the Alcoa catalyst. These workers demonstrated that dimethylaniline of 99% purity is produced in nearly quantitative yield at temperatures as low as 275°C.

The reaction conditions of the initial experiment with tetrahydropyran and aniline corresponded to that reported by Yur'ev (4) in his study of the reaction of tetrahydrofuran with this amine, namely, a catalyst temperature of 400°C. and an ether–aniline molar ratio of 1:2. The expected product, N-phenylpiperidine, was formed in 45% yield which compared with the yield of N-

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phenylpyrrolidine obtained by Yur'ev from tetrahydrofuran. It was noted, however, that the product contained no unreacted tetrahydropyran and that a considerable amount of high-boiling material and tarry residue was formed. At the same time, gaseous products were produced in an appreciable quantity, suggesting that the conditions of the reaction had been too severe. This led to a careful investigation of the influence of temperature, ratio of the reactants, and feed-rate on the yield of N-phenylpiperidine. It was found that the desired product could be obtained in a yield of 92% (based on the total ether charged) under the optimum conditions of 300°C., an ether–aniline molar ratio of 1:2, and a feed-rate of 0.321 moles of mixed reactants per 100 ml. of catalyst per hour. Comparable yields of the N-tolylpiperidines were obtained from the reaction of *m*- and *p*-toluidine with tetrahydropyran, the optimum temperature in this case being 325°C. With *o*-toluidine, on the other hand, the yield of the expected product, N-*o*-tolylpiperidine, was markedly lower and a relatively large high-boiling fraction was obtained. At 300°C., the yield was only 45%, while the maximum yield of 66% was obtained at 340°C.

Of the three N-tolylpiperidines, only the ortho compound appears not to have been reported previously in the literature. N-*p*-Tolylpiperidine and N-*m*-tolylpiperidine have been reported by Scholtz and Wassermann (3) as solids melting at 122 and 126°C., respectively. Several other workers, however, have described N-*p*-tolylpiperidine as a liquid at room temperature, and this has been confirmed in the present investigation. It is possible that the constants given in the paper by Scholtz and Wassermann are for the hydrobromide salts since they prepared their compounds by the reaction of the toluidines with 1, 5-dibromopentane. N-*m*-Tolylpiperidine, as the free base, does not appear to have been reported previously.

Since there is no reason for assuming that tetrahydropyran is more reactive than tetrahydrofuran in the reaction with aromatic amines, the high yields obtained in the present study under relatively mild conditions would suggest that Yur'ev, in his investigation of the reaction of tetrahydrofuran, either failed to determine the influence of temperature or had at his disposal an alumina catalyst of lower activity than that used in this investigation. In order to confirm this point, the reaction of aniline with tetrahydrofuran has been investigated over the Alcoa alumina catalyst and an 88% yield of N-phenylpyrrolidine was obtained at 290°C. as compared to the 45.5% reported by Yur'ev at 400°C.

EXPERIMENTAL AND RESULTS

Materials

Tetrahydropyran was kindly supplied by E. I. du Pont de Nemours and Company (Inc.). The commercial product was dried over Drierite and redistilled, the fraction boiling at 87-88°C. being used in the investigation.

Tetrahydrofuran was obtained from the Celanese Chemical Corporation. It was dried over Drierite, distilled, and a mid-cut boiling over a two-degree range retained.

Aniline (Baker and Adamson Purified Grade) was redistilled, b.p. 184-184.2°C. *o*-Toluidine (Baker and Adamson Purified Grade), *m*-toluidine (Eastman), and *p*-toluidine (Baker and Adamson Purified Grade) were used without further purification.

Catalyst

The catalyst used in all experiments reported in this paper was Alcoa Activated Alumina (Grade F-1, 4-8 mesh) supplied by the Aluminum Company of America. Following each run, the catalyst was regenerated by passing air over the catalyst bed for 24 hr. at 400°C. This served to remove adsorbed reactants and products. The presence of carbonaceous material on the catalyst was noted only after runs carried out at an elevated temperature, 375-400°C.

The activity of the catalyst, as measured by the yield of N-phenylpiperidine formed under a given set of conditions, was found to depend to a considerable extent upon its previous history. A fresh catalyst exhibited relatively low activity. Following regeneration in the manner stated, however, a slightly higher yield of product was obtained and the catalyst continued to improve in activity with successive runs and regenerations reaching a maximum at about the sixth or seventh run. This high activity was maintained during the course of the next 9 to 10 runs. (A run normally consisted of a total charge of 140 ml. of mixed reactants.) It was later found that a pretreatment of fresh catalyst by passing air over the catalyst bed for 72 hr. at 400°C. was effective in bringing it to a condition of maximum activity. All experiments reported in this paper were performed using a catalyst either pretreated in the manner described, or one which had been used for no less than six and no more than 15 runs.

The improved activity of the catalyst following prolonged heat treatment may be attributed to a conversion of some inactive boehmite present in the catalyst to γ-alumina, the catalytically active form (2). The falling-off in activity with continued usage would suggest a slow conversion of the γ-alumina into the inactive corundum form.

Apparatus and Procedure

The catalysis apparatus consisted of two zones, preheater and catalyst, each with separate heat control. The preheater was a vertical pyrex glass tube, 30 mm. O.D. and about 18 in. long, packed for a depth of 12 in. with marble chips. Heat was supplied by a 700 watt Chromel A wire heater wound on the spiral grooves of a 12 in. alundum refractory surrounding the tube. The lower end of the preheater was connected by means of a ground joint to the upper end of the catalyst tube, 30 mm. O.D. and about 34 in. in length, extending at an angle of 120° with respect to the preheater. This tube was packed with 200 ml. of catalyst which occupied a mid-section of the tube for a length of about 15 in. Heat for the catalyst zone was supplied by two heaters, similar to that used for the preheater, placed end to end. A thin copper tube was fitted snugly inside the refractory heaters to assist in maintaining a uniform temperature throughout the length of the catalyst bed. Both the preheater and catalyst zones were suitably insulated, and temperatures in each were measured by means of thermocouples movable along wells concentric with the tubes.

The reactants, mixed in the desired ratio, were introduced by means of a constant-feed device into the upper end of the preheater, where they were vaporized and preheated to the desired temperature before entering the catalyst tube. The reaction products passing from the catalyst zone were condensed by means of a Friedrich condenser and collected in a suitable receiver. All connections were made with ground joints. In order to establish equilibrium conditions, a prerun of 40 ml. was made during which temperatures and feed-rate were given final adjustment. A run usually consisted of 100 ml. of mixed reactants in addition to the prerun.

The liquid products consisted of two phases, aqueous and organic, of about the same density. The organic phase was salted out with sodium chloride, separated, and dried over sodium hydroxide. The product was carefully fractionated, using an 18 in. column packed with 3/32 in. glass helices, first under normal pressure to remove low-boiling material and unchanged cyclic ether, and finally under reduced pressure to recover excess amine. The N-arylpiperidine remaining was then distilled in an ordinary Claisen flask under reduced pressure. Some high-boiling residue usually remained in the distillation flask.

TABLE I

IDENTIFICATION OF PRODUCTS

Compound	B.p.,* °C.	n_D^{25}	Derivatives
N-Phenylpiperidine	129-132 (20 mm.)	1.5601	Picrate m.p. found: 147.5-148.5°C.† lit.: 148°C. Hydrobromide m.p. found: 235-236°C.† lit.: 235°C.
N-*p*-Tolylpiperidine	140.8-142.0 (16 mm.)	1.5502	Picrate m.p. found: 175.9-176.2°C.† lit.: 176°C.
N-*m*-Tolylpiperidine	138-139 (12 mm.)	1.5535	Picrate m.p. found: 176.3-176.6°C.† Hydrochloride calc. for $C_{12}H_{18}NCl$: Cl, 16.75% found: Cl, 16.97, 17.04%
N-*o*-Tolylpiperidine	141.2-141.9 (28 mm.)	1.5392	Picrate m.p. found: 153.8-154.1°C.† Hydrochloride calc. for $C_{12}H_{18}NCl$: Cl, 16.75% found: Cl, 16.78, 16.81%
N-Phenylpyrrolidine	135-138 (20 mm.)	1.5823 (n_D^{20}) 1.5827 (n_D^{20}) (lit.)	Picrate m.p. found: 119.5-120.0°C.† lit.: 117-118°C.

* *Uncorrected.*
† *Corrected.*

The products from the reactions of tetrahydropyran with aniline, *m*-toluidine, and *p*-toluidine, and from tetrahydrofuran with aniline, distilled over a three-degree range and were considered to be essentially pure compounds. This was further demonstrated in each case by a fractional distillation during which the boiling point and refractive index of the distillate remained constant. The product from the reaction of tetrahydropyran and *o*-toluidine, on the other hand, distilled over a much wider range and, in addition, there was a high-boiling fraction and considerable residue. This necessitated a careful fractionation of the product from each run in order to obtain the N-*o*-tolylpiperidine as a narrow-boiling fraction.

The products which have been previously reported in the literature, N-phenylpiperidine, N-*p*-tolylpiperidine, and N-phenylpyrrolidine, were identified by their boiling points and the melting points of their picrate derivatives. The new compounds, N-*o*-tolylpiperidine and N-*m*-tolylpiperidine, were converted to their hydrochloride salts which were then analyzed for chlorine gravimetrically; picrate derivatives were also prepared.

Physical constants of all products and other data for their identification are found in Table I.

Reaction of Tetrahydropyran with Aniline

The effect of temperature on the reaction of tetrahydropyran with aniline is shown in Table II. Below 300°C., a relatively low yield of N-phenylpiperidine based on ether charged was obtained. This was due to an incomplete reaction as indicated by the presence of unreacted ether and an aniline recovery in excess of 0.5 moles per mole charged. Yields based on reactants consumed, on the other hand, were well over 90%, demonstrating that under these conditions side-reactions were occurring to a minor extent. Above 350°C., the side-reactions became more extensive and resulted in the formation of a considerable amount of high-boiling material and a volatile fraction (b.p. 40-46°C.) identified as a mixture of normal pentadienes. (Some of the high-boiling material may have been formed by polymerization of these dienes.) It is evident from the data on the recovery of aniline and the yields of the product that tetrahydropyran was involved to a greater extent than aniline in these side-reactions. Nevertheless, the small reduction in the yields based on aniline consumed would indicate that this reactant also enters into side-reactions at

TABLE II

EFFECT OF TEMPERATURE ON THE REACTION OF TETRAHYDROPYRAN WITH ANILINE
(Ether–aniline molar ratio: 1: 2)
(Feed rate: 0.321 moles of mixed reactants per hour per 100 ml. of catalyst)

Run No.	Temp., °C.	Moles recovered per mole charged		Residue, gm. per 100 gm. N-PP**	% Yield of N-PP** based on:		
		THP*	Aniline		THP* charged	THP* consumed	Aniline consumed
57	290	0.086	0.563	3.1	84.7	92.6	94.5
14	300	0.023	0.499	3.8	92.0	94.0	93.3
11	310	0.016	0.500	3.6	92.0	93.2	92.0
16	325	0.000	0.504	4.6	91.0	91.0	91.8
17	335	0.000	0.502	4.3	91.8	91.8	91.0
18	350	(0.004)†	0.521	10.9	84.1	84.1	86.2
21	375	(0.043)†	0.550	14.1	71.9	71.9	76.0
2	400	(0.078)†	0.662	††	58.5	58.5	86.6

* *Tetrahydropyran.*
** *N-Phenylpiperidine.*
† *Mixed pentadienes (b.p. 40-46°C.) expressed as moles per mole THP charged.*
†† *Not determined.*

the more elevated temperatures. Maximum yields of N-phenylpiperidine were obtained in the temperature range 300-335°C., where a favorable balance was achieved between the extent of conversion and the formation of the dienes and other side-reaction products.

The effect of the ratio of the reactants on the yield of N-phenylpiperidine is shown in Table III. It is apparent from these results that an excess of aniline was required to achieve high yields of the desired product. This excess need not be large, however; at 325°C., an 87.1% yield (based on ether charged) was obtained using an ether–aniline ratio of 1: 1.2 compared to 91.0% when this ratio was 1: 2. The data presented in this table provides further evidence that side-reactions mostly involve the ether reactant. At 335°C., a 1: 1 molar ratio of reactants gave a yield of N-phenylpiperidine based on ether consumed which was 10% lower than that based on aniline consumed. This difference becomes as great as 25% when the ether–aniline ratio was 2: 1.

TABLE III

Effect of ratio of reactants on the reaction of tetrahydropyran with aniline
(Feed rate: 0.318 ± 0.003 moles of mixed reactants per hour per 100 ml. of catalyst)

Run No.	Molar ratio, THP: aniline	Diene fraction, moles per mole THP	Residue, gm. per 100 gm. N-PP	% Yield of N-PP based on: THP charged	THP consumed	Aniline charged	Aniline consumed
Temperature: 300°C.							
14	1:2	0.00	3.8	92.0	94.0		93.3
47	1:1.2	0.00	4.1	78.8	93.8		96.3
33	1:1	0.00	3.3	73.8	91.6	73.8	97.6
42	2:1	0.00	6.9		82.8	89.4	89.4
Temperature: 335°C.							
17	1:2	0.00	4.3	91.8	91.8		91.0
35	1:1	0.015	6.0	81.8	84.6	81.8	94.9
40	2:1	0.031	17.2		63.0	88.7	88.7

Feed-rate was found not to be an important variable in the reaction. At 300°C. and an ether–aniline ratio of 1: 2, an increase in feed-rate from 0.321 moles of mixed reactants per hour per 100 ml. of catalyst to 1.28 moles resulted in a decrease in the yield of N-phenylpiperidine of only 5%. The yields based on ether and aniline consumed were not affected.

Reaction of Tetrahydropyran with the Toluidines

The results of this study are summarized in Table IV. Excellent yields of N-tolylpiperidines were obtained with *m*- and *p*-toluidine. With *o*-toluidine, on the other hand, yields were much lower and high-boiling material was formed in considerable quantity at temperatures as low as 325°C. This result is indeed not surprising since Scholtz and Wassermann (3) have shown

TABLE IV

REACTION OF TETRAHYDROPYRAN WITH THE TOLUIDINES

(Ether–toluidine molar ratio: 1: 2)

(Feed rate: 0.285 moles of mixed reactants per hour per 100 ml. of catalyst)

Run No.	Temp., °C.	Moles recovered per mole charged		High-boiling fraction and residue, gm. per 100 gm. N-TP*	% Yield of N-TP* based on:		
		THP	Amine		THP charged	THP consumed	Amine consumed
p-Toluidine							
53	300	0.038	0.511	4.0	90.8	94.1	91.5
52	325	0.000	0.501	3.6	92.5	92.5	92.5
m-Toluidine							
58	325	0.000	0.495	4.8	94.3	94.3	92.6
o-Toluidine							
55	300	0.290	0.758	6.8	44.9	62.1	83.8
54	325	0.086	0.653	11.3	61.3	67.0	82.8
56	340	0.019	0.618	14.6	66.3	67.5	82.7

* *N-Tolylpiperidine.*

that the reaction of 1, 5-dibromopentane with *o*-toluidine failed to give the expected N-*o*-tolylpiperidine, but instead, yielded an open-chain compound identified as 1, 5-di-*o*-toluinopentane. They attributed this result to the steric effect of the ortho methyl group; the reduced yield of N-*o*-tolylpiperidine in the present investigation may be similarly explained.

Reaction of Tetrahydrofuran with Aniline

The results of three experiments involving these reactants are given in Table V. It is apparent that even milder conditions are effective for this reaction. This would clearly indicate that the temperature of 400°C. used by Yur'ev in his investigation of the reaction was much too high and that extensive side-reactions were responsible for his low yield of 45.5%.

TABLE V

REACTION OF TETRAHYDROFURAN WITH ANILINE

(Ether–aniline molar ratio: 1: 2)

(Feed rate: 0.342 moles of mixed reactants per hour per 100 ml. of catalyst)

Run No.	Temp., °C.	Ether recovered: moles per mole charged	% Yield N-phenylpyrrolidine based on ether charged
THF 4	290	0.01	88.0
THF 3	300	0.00	79.6
THF 1	310	0.00	73.9

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REFERENCES

1. Evans, T. H. and Bourns, A. N. Can. J. Technol. 29: 1. 1951.
2. Feachem, G. and Swallow, H. T. S. J. Chem. Soc. 267. 1948.
3. Scholtz, M. and Wassermann, E. Ber. 40: 852. 1907.
4. Yur'ev, Yu. K. and Minkina, G. A. J. Gen. Chem. (U.S.S.R.), 7: 2945. 1937.
5. Yur'ev, Yu. K., Pervova, E. Ya., and Sazonova, V. A. J. Gen. Chem. (U.S.S.R.), 9: 590. 1939.