EXPERIMENTAL

Melting points were determined on a Fisher-Johns hot stage microscope, and are uncorrected. Microanalyses were performed by Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England. Since the same procedure was often used to prepare several compounds, details are given below for representative experiments.

Ethyl-β-(1-nitrocyclohexyl)propionate (V). To a mechanically stirred solution of 129.2 g. (1.0 mole) of nitrocyclohexane, 50 ml. of *t*-butyl alcohol, and 12 g. of a 35% methanolic solution of Triton B was added dropwise, over 2 hr., 100.1 g. (1.0 mole) of redistilled ethyl acrylate. The reaction was mildly exothermic, and the temperature was maintained at 35–40° with a cold water bath. When the addition was completed, the mixture was stirred at room temperature for 5 hr. and allowed to stand overnight. The mixture was acidified with dilute hydrochloric acid and extracted with chloroform. After washing with water and drying over magnesium sulfate, the extracts were concentrated and the residue distilled through a short Vigreux column. The nitroester distilled as a pale green oil at 139–141°/3 mm., 117–118°/0.6 mm., and weighed 210.5 g. (91.6%).

β-(1-nitrocyclohexyl)propionic acid (VI).[8] The nitro-ester (54 g.) was refluxed with a solution of 40 g. of sodium hydroxide in 350 ml. of water for 10 hr. After cooling in ice, the solution was acidified with concentrated hydrochloric acid and allowed to stand in the refrigerator. The collected solid weighed 39 g. (83%). Recrystallized from water, it yielded white plates, m.p. 93.0–93.6°. Recrystallization from ethanol-water raised the melting point to 93.7–94.2°.

Ethyl γ-(1-nitrocyclohexyl)butyrate (VII). Thionyl chloride was purified by successive distillations from cholesterol, quinoline, and linseed oil. The nitro-acid (20 g.) was refluxed with 100 ml. of thionyl chloride for 4 hr., and the excess thionyl chloride was evaporated, finally by distilling 50 ml. of dry benzene from the solution. The acid chloride was generally used without further purification; in one run it was distilled *in vacuo*, b.p. 105–109°/0.1 mm. When a sample was treated with water, it regenerated the original acid.

A solution of the acid chloride in 60 ml. of anhydrous ether was added to an ethereal solution of excess diazomethane. After standing overnight, the ether was removed at reduced pressure, leaving the diazoketone as an orange oil. It was heated to reflux in 200 ml. of absolute ethanol, while over a period of 48 hr. a slurry of silver oxide (from 10 g. of silver nitrate) in ethanol was added in portions. The mixture was filtered and the filtrate distilled. The nitro-ester was collected at 128–131°/0.1 mm., and weighed 17.8 g. (73.6%).

1-Azaspiro[4,5]decanone-2 (XII).[3-6] A solution of 40 g. (0.175 mole) of ethyl-β-(1-nitrocyclohexyl)propionate in 125 ml. of ethanol was hydrogenated over Raney nickel at 38 pounds pressure and room temperature. After 6 hr., 0.55 mole of hydrogen had been absorbed. The catalyst was removed by filtration and the filtrate refluxed overnight. Distillation of the alcohol left a solid residue, which was collected and washed with a little ether. The crystals weighed 22 g. and melted at 132–132.5°. A second crop of 3.9 g. was isolated from the filtrate by sublimation, bringing the total yield to 96%. The lactam was easily purified by recrystallization from 60–70° petroleum ether or by sublimation at 100°/0.03 mm., though the melting point remained unchanged.

3-(1-Aminocyclohexyl)propanol-1. A solution of 25.9 g. (0.113 mole) of ethyl β-(1-nitrocyclohexyl)propionate in 25 ml. of anhydrous ether was added with stirring over 2 hr. to a solution of 11.8 g. (0.31 mole) of lithium aluminum hydride in 200 ml. of ether. After stirring and refluxing for 2 hr., the mixture was treated with 20 ml. of ethyl acetate, then with saturated aqueous sodium sulfate. Magnesium sulfate was added to coagulate the alumina, and the mixture filtered and washed with hot ethanol. The filter cake was digested three times with hot alcohol, and the combined filtrates dried over magnesium sulfate. Concentration and vacuum distillation gave the amino-alcohol as a pale green oil, b.p. 98–100°/0.15 mm., weighing 11.0 g. (62%). After standing for a few hours, it crystallized to white plates, which, recrystallized from ether, melted at 69.5–70.5°.

Anal. Calcd. for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.80; H, 12.01; N, 8.97.

The *O,N-diacetate*, prepared with acetic anhydride in pyridine, melted at 96.5–97.5° after successive recrystallizations from cyclohexane and ether.

Anal. Calcd. for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 65.54; H, 9.41; N, 5.93.

The *O,N-di-p-toluenesulfonate* was prepared by the Hinsburg procedure.[9] After two recrystallizations from ethanol, it melted at 176.5–177.5°.

Anal. Calcd. for $C_{23}H_{31}NO_5S_2$: C, 59.33; H, 6.71; N, 3.01; S, 13.77. Found: C, 59.49; H, 6.63; N, 2.95; S, 13.53.

γ-(1-cyclohexenyl)butyramide (XIV). γ-(1-cyclohexenyl-butyric acid[10] (8.2 g.) was esterified with an ethereal solution of diazomethane from 25 g. of nitrosomethylurea. After removal of the ether, the residual ester was taken up in 60 ml. of methanol, saturated at 0° with dry ammonia, and heated at 125° overnight in a sealed bomb. After charcoal treatment and filtration, the methanol was evaporated to a small volume and the amide precipitated with water. Recrystallized from ethyl acetate-petroleum ether, it melted at 97–98°.

Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.66; H, 10.04; N, 8.05.

Acid cyclization of amide. Two hundred fifty mg. of γ-(1-cyclohexenyl)butyramide was stirred into 12 g. of polyphosphoric acid and heated at 120–130° for 10 min. This solution was poured into a mixture of ice and sodium hydroxide solution, stirred until homogeneous, and extracted with chloroform. The extracts were washed with water, dried over sodium sulfate, and evaporated. The solid residue weighed 250 mg., and after recrystallization from 60–70° petroleum ether, melted at 116.5–118°, alone or admixed with a sample of 1-azaspiro[5,5]undecanone-2 (XIII).

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Preparation of Dialkylanilines by the Reaction of Bromobenzene with Sodium Amide and Dialkylamines[1]

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Reactions have been reported[3] of the monobro-

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(2) American Enka Fellow, 1954–55; R. J. Reynolds Fellow, 1955–56. This note is based on the Ph.D. thesis of T. K. Brotherton, October, 1956.

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monaphthalenes with sodium amide in refluxing piperidine to form, in high total yields, mixtures of the two *N*-naphthylpiperidines. There is evidence that these reactions proceed by the elimination-addition (benzyne) mechanism.[3,4] In connection with the above work, bromobenzene was submitted to the action of the sodium amide-piperidine reagent and *N*-phenylpiperidine was obtained in 99% yield. This observation suggested that the reaction of bromobenzene with sodium amide in refluxing secondary amines might be a general method for the preparation of dialkylanilines. We have found that the method is indeed general, but yields are for the most part not especially high. Our results are summarized in Table I.

TABLE I

YIELDS OF DIALKYLANILINES FROM BROMOBENZENE, SODIUM AMIDE, AND DIALKYLAMINES

Secondary Amine Used	Reflux Time, Hr.	Yield of Dialkylaniline, %
Piperidine	2	99
	1	82
	0.17	51
Diethylamine	2	53
	3.75	46
	16	64
Diisopropylamine	2	22[a]
Di-*n*-butylamine	2	67
Morpholine	2	46[b]

[a] 58% of bromobenzene was recovered. [b] 8% of bromobenzene was recovered.

The reaction of bromobenzene with sodium amide in refluxing aniline was also tried. Diphenylamine (25%) and triphenylamine (4%) were obtained, along with small amounts of other products which were not identified.

Reactions of this general type have been reported before. Thus, Wittig and Merkle[5] obtained a 16% yield of *N*-phenylpiperidine from iodobenzene and lithium piperidide in ether. Even more similar to the present work is the preparation, by Seibert and Bergstrom,[6] of *N*-cyclohexylaniline in 42% yield by the reaction of bromobenzene with potassium amide in cyclohexylamine at 120–130°.

Presumably all these reactions occur by the benzyne mechanism. If so, the recovery of much bromobenzene from the reaction with diiospropylamine would suggest that it is a dialkylamide ion rather than a simple amide ion (NH_2^-) which removes a proton from the position *ortho* to the bromine, and that the diisopropylamide ion is relatively inefficient in this function owing to front-side steric hindrance.[7] The fact that smaller yields were obtained with other dialkylamines than with piperidine is perhaps a further consequence of front-side steric interactions which retard the combination of benzyne with the bulkier dialkylamide ions (or dialkylamines), allowing time for the benzyne to undergo side reactions with eventual formation of tarry by-products.[8]

N-Phenylpiperidine is also formed by the reaction of bromobenzene with sodium metal in refluxing piperidine; however, in this case the yield is only 67%.

Earlier[4] it was found that the sodium amide–piperidine reagent acts upon 1-bromo-2-methylnaphthalene to form 2-methylnaphthalene in 81% yield. A similar debromination has now been observed in the reaction of 2-bromomesitylene with this reagent: mesitylene is formed in 53% yield with 24% recovery of unreacted 2-bromomesitylene. 2-Bromomesitylene, like 1-bromo-2-methylnaphthalene, is structurally unable to be converted into a benzyne derivative. In the reaction of such a compound with the sodium amide–piperidine reagent, reductive debromination appears to occur more readily than direct displacement of the bromine by piperidide ion.

EXPERIMENTAL

Reaction of bromobenzene with sodium amide and piperidine. A mixture of sodium amide (7.8 g., 0.2 mole) and piperidine[9] (30 cc.) was refluxed for 15 min. Bromobenzene (15.7 g., 0.1 mole) was then added dropwise through the top of the condenser. A vigorous reaction ensued with the evolution of ammonia, but the reaction subsided when all the bromobenzene had been added. The resulting mixture was refluxed for 2 hr., cooled, and cautiously treated with 25 cc. of water and 25 cc. of benzene. The layers which formed were separated and the benzene layer was washed with three 25-cc. portions of 10% hydrochloric acid. The acid extracts were combined and made strongly basic by the addition of concentrated sodium hydroxide solution. The oil layer which formed was taken up in 15 cc. of ether and the aqueous layer was washed with an additional 15 cc. of ether. The two ether solutions were combined and distilled; the main fraction of the distillate was 16.05 g. (98.8%) of *N*-phenylpiperidine, b.p. 93–97° (3–4 mm.), n_D^{25} 1.5593. (Authentic *N*-phenylpiperidine was found to have b.p. 98° (5 mm.), n_D^{23} 1.5606.) The identity of the product was further verified by formation of the methiodide, m.p. 146.5–148° not depressed on admixture with authentic *N*-phenylpiperidine methiodide.[10]

Reactions by the same procedure but with shorter periods of reflux (after addition of the bromobenzene) gave lower yields of *N*-phenylpiperidine as shown in Table I. When the reagents were mixed with no prior refluxing of the sodium amide and piperidine, no detectable amount of *N*-phenylpiperidine was formed during 10 min. refluxing or during 24 hr. at room temperature.

Reactions of bromobenzene with sodium amide and other dialkylamines. Each amine was a commercial product (generously furnished by Union Carbide Chemicals Co.)

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which was dried by azeotropic distillation with benzene and then purified by distillation. The procedure (including quantities of reactants) was in each case as described for the reaction with piperidine. Characteristics of the products were as follows: *N,N*-Diethylaniline: b.p. 62–66°/3 mm., n_D^{24} 1.5394 (lit.[11,12] b.p. 70°/3 mm., n_D^{22} 1.5410). *N,N*-Diisopropylaniline: b.p. 95.5°/12 mm., n_D^{20} 1.5222 (lit.[13] b.p. 98–100°/13 mm). *N,N*-Di-*n*-butylaniline: b.p. 103.5–106° (3.5 mm.), n_D^{20} 1.5182. The picrate, crystallized from ether, had m.p. 124° (lit.[14] m.p. 124°) not depressed on admixture with the picrate of authentic *N,N*-di-*n*-butylaniline. *N*-Phenylmorpholine: b.p. 87–92°/3–4 mm., m.p. 52–53° after crystallization from an ethanol-ether mixture (lit.[15] m.p. 57–58°).

Reaction of bromobenzene with sodium amide and aniline. Bromobenzene (15.7 g., 0.1 mole), sodium amide (11.7 g., 0.3 mole) and 35 cc. of purified aniline were allowed to react by the procedure described for the reaction with piperidine. After water had been added to the reaction mixture, it was made acidic by addition of hydrochloric acid and then was extracted with five 150-cc. portions of benzene. The combined benzene washings were distilled until the boiling point reached 80° and then were treated with anhydrous hydrogen chloride. The purple solid which formed was collected on the suction filter and then was treated with sodium hydroxide solution. The resulting product was separated by steam distillation. Diphenylamine (4.3 g., 25.4%), m.p. 52–52.5°, not depressed on admixture with authentic diphenylamine, was so obtained. The benzene filtrate was distilled and two fractions of interest were obtained: a yellow oil, b.p. 100–106° (2–3 mm.), wt. 3.9 g., and a mushy solid, b.p. 106–161° (2–3 mm.), wt. 2.8 g. By trituration of the first fraction with petroleum ether (b.p. 30–60°), 1.1 g. of a sublimable white solid, m.p. 205–210° with decomposition, was obtained, but this product was not identified. Cooling the filtrate to −78° caused 0.61 g. of a sublimable solid, m.p. 33–35°, to separate; this was not identified. From the second fraction, 0.33 g. (4.4%) of triphenylamine, m.p. 126–127° not depressed on admixture with authentic triphenylamine, was obtained by crystallization from petroleum ether (b.p. 30–60°). A yellow oil, n_D^{18} 1.6431, remained on evaporation of the mother liquor from the triphenylamine crystallization.

Reaction of 2-bromomesitylene with sodium amide and piperidine. 2-Bromomesitylene (19.9 g., 0.1 mole), sodium amide (7.8 g., 0.2 mole) and 30 cc. of piperidine were allowed to react by the procedure described above for the bromobenzene-sodium amide-piperidine reaction. From the neutral product fraction, 6.4 g. (53.2%) of mesitylene, b.p. 75–78° (40 mm.), n_D^{24} 1.4987 (authentic mesitylene has b.p. 79.8°/40 mm., n_D^{18} 1.4954) and 4.8 g. (24.1% recovery) of 2-bromomesitylene, b.p. 106–109°/17 mm., n_D^{24} 1.5480 (authentic 2-bromomesitylene has b.p. 108–110°/17–18 mm., n_D^{24} 1.5484). No basic product could be isolated.

Reaction of bromobenzene with piperidine and sodium metal. Sodium metal (2.3 g., 0.1 mole) and piperidine (20 cc.) were combined and heated at reflux for 15 min. Bromobenzene (7.9 g., 0.05 mole) was then added through the condenser and the resulting mixture was refluxed for 2 hr. Water (25 cc.) was cautiously added to the cooled reaction mixture; there was little evidence of residual sodium. The neutral and basic product fractions were separated by common extraction procedures. The basic fraction yielded 5.2 g. (60.7%) of *N*-phenylpiperidine, b.p. 95–98° (5 mm.), n_D^{25} 1.5590. The neutral fraction furnished 0.9 g. of an unidentified yellow oil b.p. 65–68° (40 mm.).

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Preparation of Tetramethylene Dibromide and Chlorobromide

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In the course of a synthetic study relatively large quantities of tetramethylene dibromide and chlorobromide were required, and an attempt was made to develop inexpensive methods for the preparation of these substances.

For the preparation of tetramethylene dibromide, the reaction of tetramethyleneglycol with hydrogen bromide (yield, 70%),[1] with hydrogen bromide in the presence of concentrated sulfuric acid,[2,3] or with phosphorus tribromide (55–60%)[4] has been described. Since tetrahydrofuran has become easily available, its reaction with hydrogen bromide (71%)[5–7] or with hydrogen bromide and concentrated sulfuric acid (77–82%)[8,9] has been suggested as an attractive alternative. A third method is the bromination of butane in the presence of zinc acetate (85%).[10] It has now been found that the reaction of tetrahydrofuran with sodium bromide and concentrated sulfuric acid represents the easiest method. Under the conditions specified herein, this reaction gives a yield of 86%.

Most of the syntheses of tetramethylene chlorobromide have been based on tetrahydrofuran and consist of two steps, its transformation into tetramethylene chlorohydrin (50–60%) and the treatment of the latter with phosphorus tribromide

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