

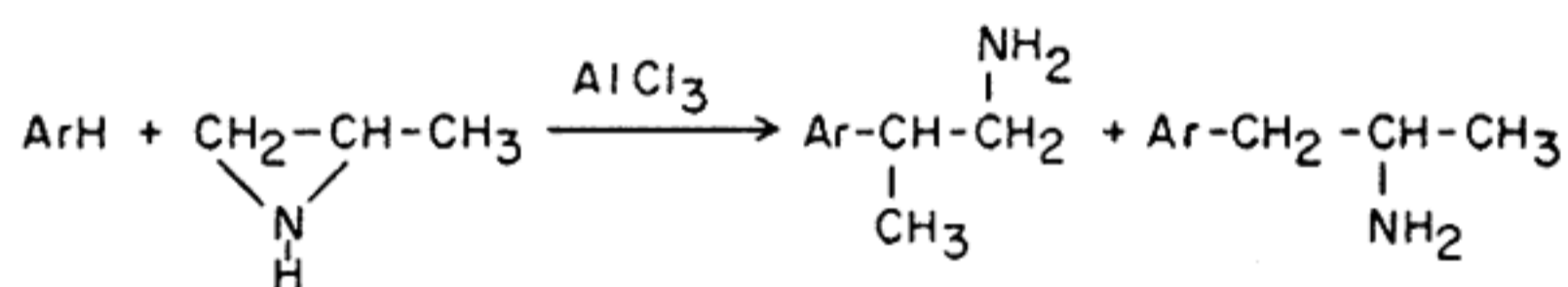
Friedel Crafts Reactions of Three-Member Heterocycles II.

Alkylation of Aromatic Compounds with Aziridines

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The Friedel Crafts reaction of propylenimine with symmetrical arenes in the presence of aluminum chloride was investigated. Electron donating substituents increase the α -methyl- β -phenethylamine/ β -methyl- β -phenethylamine ratio, while increasing the temperature has the opposite effect. In the reaction of chlorobenzene or toluene with aziridine, the nature of the substituent has little effect on the *ortho/para* ratio.

It has been established by Braz that β -phenethylamines can be prepared by the reaction of benzene and its derivatives with aziridines (1,2):



The reactions of propylenimine with benzene, *p*-xylene, and mesitylene at reflux temperature in the presence of aluminum chloride were investigated in order to measure the effect of electron-donating substituents upon the chain isomer distribution. The reaction of propylenimine with benzene at 170° was studied to determine the effect of temperature upon the isomer distribution. The results are listed in Table I.

Ethylenimine was reacted with toluene and chlorobenzene at reflux temperature in the presence of aluminum chloride. The results are shown in Table II.

The aluminum chloride-coordinated aziridine ring may be considered to undergo ring opening to give the most substituted carbonium ion which then attacks the aromatic ring resulting in β -substituted β -phenethylamine; or alternatively, the aromatic component of such Friedel Crafts condensation may be considered to function as a nucleophile in which π electrons attack the aluminum chloride-coordinated aziridine ring resulting in α -substituted β -phenethylamines.

From the above results it is apparent that both mechanisms are working simultaneously. This is evident


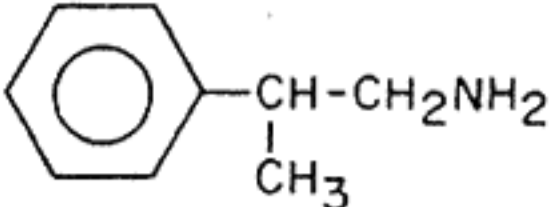
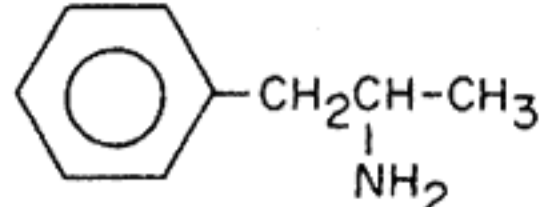

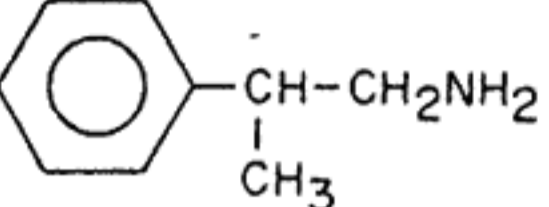
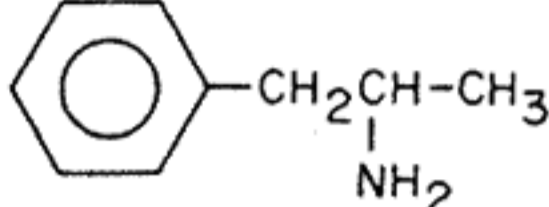
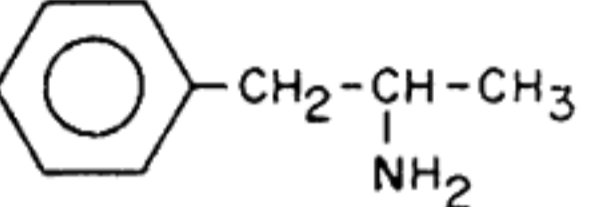
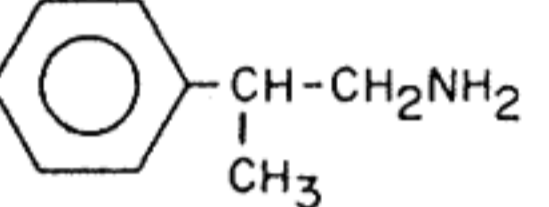
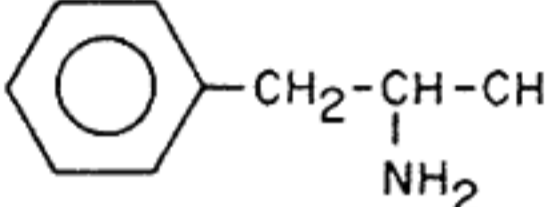
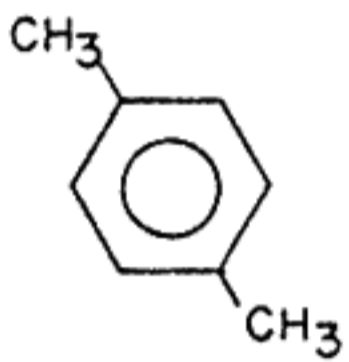
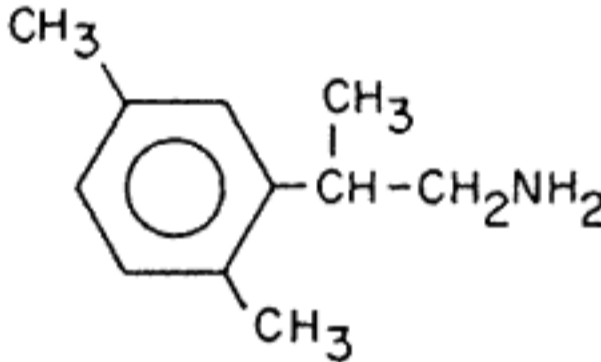
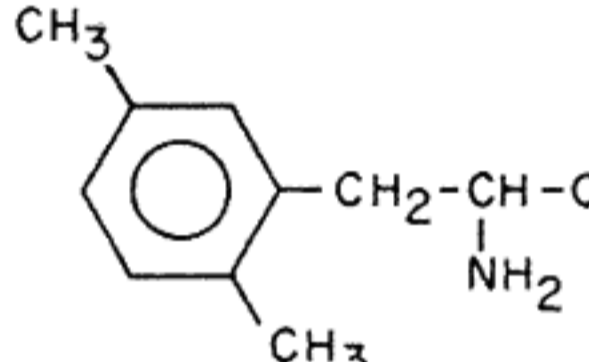
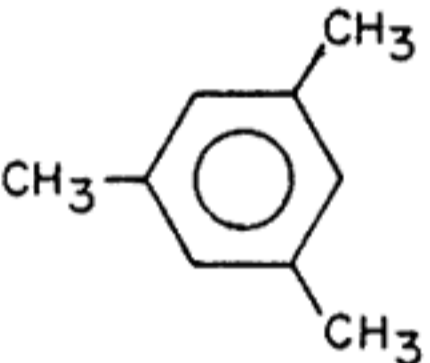
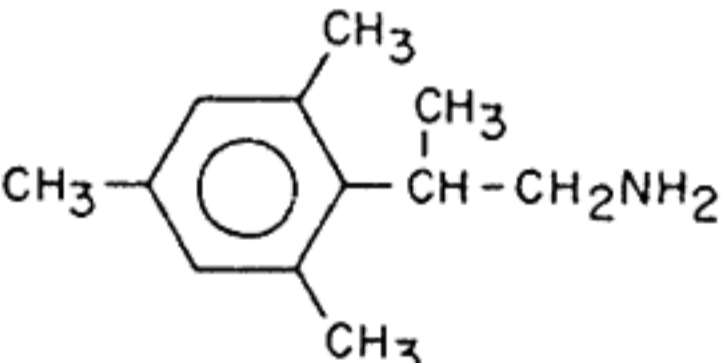
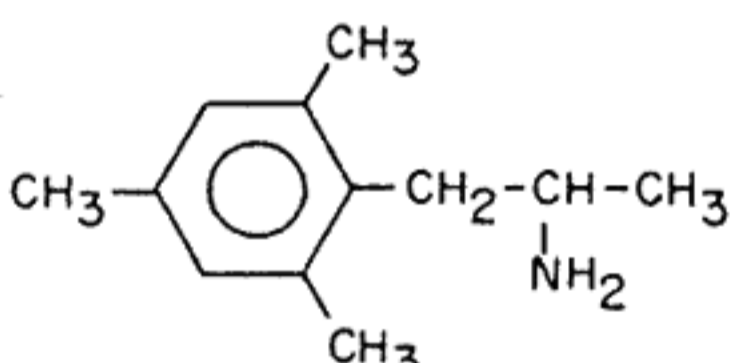
from the greater selectivity of the reaction of propylenimine at 170° than at reflux temperature. (If the reaction proceeded entirely by the carbonium ion mechanism, one would expect to observe less selectivity at the high temperature). The ring opening must have a higher energy of activation than the nucleophilic attack of the aromatic compound on the coordinated aziridine ring and is favored by high temperature. In addition the increasing percentage of α -methyl β -phenethylamines with increasing nucleophilicity of the aromatic hydrocarbon in the reactions of propylenimine with benzene, *p*-xylene, and mesitylene (despite the higher reflux temperatures) indicates the duality of mechanism in the alkylation of aromatics with aziridine.

EXPERIMENTAL

Reaction of Propylenimine with Benzene (Reflux).

To 10.2 g. of anhydrous aluminum chloride (0.077 mole) and 18 ml. of benzene in a 100-ml. 3-neck flask equipped with a magnetic stirrer was added 2.85 ml. propylenimine (0.04 mole) in 14 ml. benzene at 10° with stirring. The addition required about 15 minutes. The ice bath was removed after 0.5 hour of stirring, and the reaction mixture was refluxed for 24 hours. It was then poured into 50 ml. of ice water. The benzene layer was discarded and the aqueous layer was made alkaline by the addition of solid potassium hydroxide until most of the white precipitate had gone into solution. The water layer was then extracted with 20 ml. of ether and three successive 10 ml. portions, and the ether layer was dried over anhydrous potassium hydroxide. The ether was removed under vacuum and the residue, which was almost entirely α -methylphenethylamine (amphetamine) and β -methylphenethylamine (pervitin), weighed 0.85 g. (15.7% yield of

TABLE I

Aromatic Compound	Reaction Time	Temp. (a)	Products (b)		Yield (%) (c)
	24 hr.	reflux			15.7
			78%	22%	
	22 hr.	170°			31
			89%	11%	
	7 hr.	170°			82
			0%	100%	
	16 hr.	reflux			19
			73%	27%	
	4½ hr	reflux			38
			57%	43%	

(a) Reactions at 170° were performed in small steel bombs. (b) Product ratios were determined by gas chromatography (6' x 1/8" 10% SE-30 columns). The data for each run represent an average of three determinations. (c) No attempt was made to recover propylenimine from the reaction mixture.

methylphenethylamines). The product ratio was determined by g.l.p.c. (6' x 1/8" 10% SE-30 columns).

Authentic amphetamine was obtained from Aldrich, and pervitin was prepared by the reaction of allylamine with benzene in the presence of aluminum chloride (3). Both compounds are g.l.p.c. pure.

Reaction of Propylenimine with Benzene at 170°.

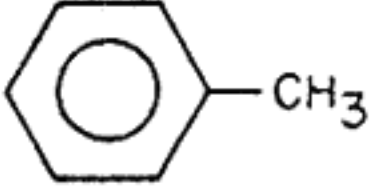
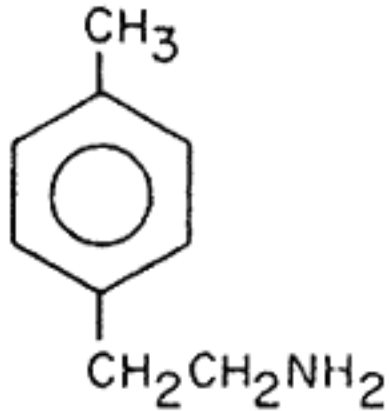
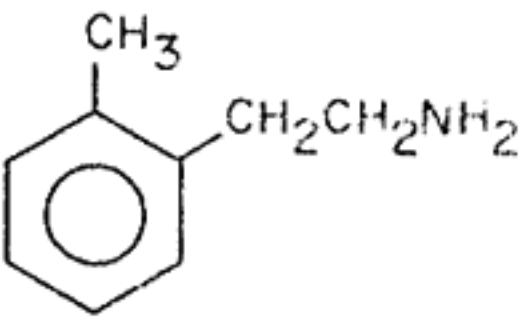
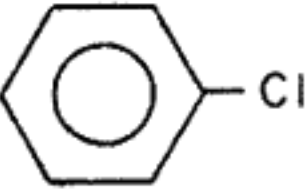
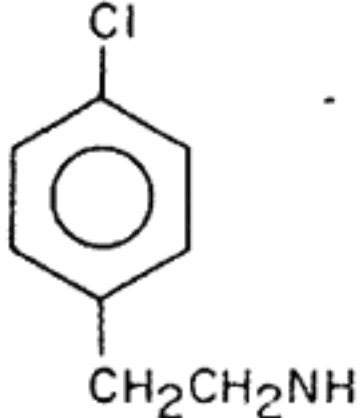
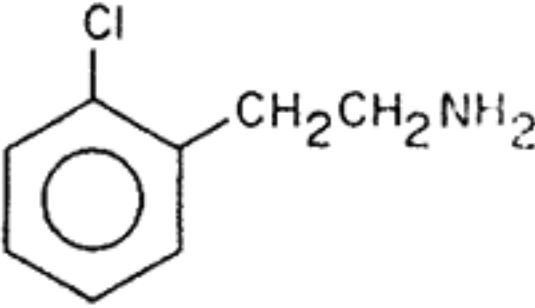
This reaction is at 0.15 x the scale of the previous one. To a stainless steel tube cooled in ice water was added 1.5 g. of anhydrous aluminum chloride, 3.2 ml. of benzene, and 0.43 ml. of propylenimine in 1.5 ml. of benzene. The reaction mixture was heated in an oil bath at 170 ± 0.1° for seven hours.

As a control, 0.4 ml. of pure amphetamine was added in benzene solution to the same amount of aluminum chloride and benzene, and heated under the same conditions. Both tubes were cooled in an ice bath and worked up in the same manner as before. The residue from the propylenimine reaction weighed 0.50 g. (62% yield). A duplicate reaction was run for 22 hours and gave the same isomer distribution but a 31% yield. The pure amphetamine does not isomerize under the reaction conditions.

Reaction of Propylenimine with *p*-Xylene.

To 5.33 g. of aluminum chloride (0.04 mole) in a 100-ml. 3-neck flask was added 20 ml. *p*-xylene with magnetic stirring. To the stirring mixture was added a solution of 2.85 ml. of

TABLE II

Aromatic Compound	Reaction Time	Products (a)	Yield (%)	
	5 hr.	 50%	 50%	55
	16 hr	 45%	 55%	69

(a) Product ratios were determined by gas chromatography and confirmed by comparison of infrared spectra with those of authentic mixtures.

propylenimine (0.04 mole) in 15 ml. *p*-xylene dropwise. The reaction mixture was then refluxed for 16 hours with stirring. The reaction was worked up as before, and the yield of methyl-(2,5-dimethylphenyl)ethylamines was 1.2 g. or 19% of theoretical. The reference compound, β -methyl-(2,5-dimethylphenyl)ethylamine, was prepared by adapting the method of Weston, Ruddy, and Suter in reacting the *p*-xylene with allylamine (3). The yield was 2.1 g. (65% of theoretical) and is g.l.p.c. pure, b.p. 106° at 5 mm; n.m.r. gives correct integration.

Anal. Calcd. for C₁₁H₁₇N: C, 80.91; H, 10.50; N, 8.58. Found: C, 80.47; H, 10.66; N, 8.43.

Reaction of Propylenimine with Mesitylene.

To 5.33 g. of aluminum chloride (0.04 mole) in a 100-ml. 3-neck flask cooled by an ice water bath was added 25 ml. mesitylene. To the stirring mixture was added a solution of 2.85 ml. propylenimine (0.04 mole) in 15 ml. mesitylene dropwise. The mixture was refluxed with stirring for 4½ hours and poured into ice water. The yield of the isomeric methyl(2,4,6-trimethylphenyl)ethylamines was 2.7 g. or 38% of theoretical. The reference compound, β -methyl-(2,4,6-trimethylphenyl)ethylamine, was prepared by reacting the hydrocarbon with allylamine in the presence of aluminum chloride (3). The yield was 4.4 g. (62% of theoretical) and is g.l.p.c. pure, b.p. 124° at 6 mm; n.m.r. gives correct integration.

Anal. Calcd. for C₁₂H₁₉N: C, 81.30; H, 10.80; N, 7.90. Found: C, 81.11; H, 10.70; N, 7.71.

Reaction of Ethylenimine with Toluene.

To a 500-ml. 3-neck flask equipped with a reflux condenser and magnetic stirrer was added 120 ml. of toluene and 51.0 g. of aluminum chloride (0.38 mole). To the vigorously stirring mixture cooled by an ice bath was added a solution of 10.3 ml. ethyl-

enimine (0.2 mole) in 80 ml. toluene over a 30-minute period. The ice bath was removed upon completion of the addition, and the mixture was refluxed for five hours. The reaction mixture was worked up in the usual manner. The yield of tolylethylamines was 14.8 g. or 55% of theoretical. The reference compound (*o*-tolyl)ethylamine is available from K and K Laboratories.

Reaction of Ethylenimine with Chlorobenzene.

To 10.2 g. of aluminum chloride (0.077 mole) in a 100-ml. 3-neck flask was added 25 ml. chlorobenzene with magnetic stirring and ice water bath cooling. To the stirring mixture was added 2.1 ml. ethylenimine (0.04 mole) in 15 ml. chlorobenzene dropwise. The reaction mixture was refluxed for 16 hours with stirring and worked up as usual. The yield of chlorophenylethylamines was 4.3 g. or 69.4% of theoretical. Both reference compounds are commercially available, the 2-(*o*-chlorophenyl)ethylamine from K and K Laboratories, and the 2-(*p*-chlorophenyl)ethylamine from Aldrich.

REFERENCES

- (1) G. I. Braz, *Dokl. Akad. Nauk SSSR*, 87, 589 (1952).
- (2) G. I. Braz, *ibid.*, 87, 747 (1952).
- (3) A. W. Weston, A. W. Ruddy, and C. M. Suter, *J. Am. Chem. Soc.*, 65, 674 (1943).