[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Synthesis of Arylpropylamines. I. From Allyl Chloride[1]

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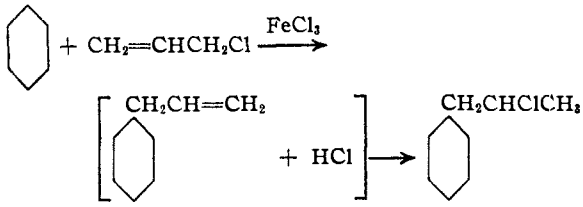
The isolation and proof of structure of the hormone epinephrine (generally attributed to Abel[3]) has led in succeeding years to the synthesis of many similar compounds which have the common property of increasing the blood pressure, but may also exhibit other varied and interesting physiological effects. Inasmuch as benzedrine, 1-phenyl-2-propylamine, and its derivatives were found to be among the most important of the pressor amines,[4] this group was selected for the present study of new compounds possessing potential pressor activity.

In 1933 Nenitzescu and Isacescu[5] synthesized 2-chloro-1-phenylpropane from benzene, allyl chloride, and ferric chloride



A by-product of the reaction was 1,2-diphenylpropane, evidently formed by further reaction of 2-chloro-1-phenylpropane with benzene. We have applied successfully the technique of Nenitzescu and Isacescu to other aromatic compounds. Both chlorobenzene and bromobenzene gave *ortho* and *para* halogenated arylchloropropanes with allyl chloride, but fluorobenzene and anisole gave only the *para* isomers in detectable amounts.

Truffault[6] found that aromatic compounds add to allyl chloride in the presence of sulfuric acid or oleum to form 2-aryl-1-chloropropanes. Truffault's experiments were repeated in this Laboratory using benzene and chlorobenzene, respectively, as the aromatic reactants. In the case of chlorobenzene, an isomer was formed as well as 2-(*p*-chlorophenyl)-1-chloropropane which Truffault reported. The ethers, anisole and veratrole, failed to add to allyl chloride by this method.

It was possible to prepare a number of arylchloropropanes, many of them new, from allyl chloride by these techniques. These compounds (Table I) are suitable as intermediates in the synthesis of arylpropylamines by ammonolysis with ammonia or amines. The aminations were carried out in an autoclave at 125–160° for reaction times of four to nine hours. In some cases aqueous solutions of ammonia or methylamine were used, but alcoholic solutions resulted in somewhat better yields and mixtures containing fewer by-products. The principal advantage of alcoholic solutions is complete homogeneity of the reaction mixture.

By-products in the reaction[7] are the alcohol and ethyl ether corresponding to the halide undergoing reaction, in addition to higher amines. The formation of higher amines is suppressed by using a large excess of the aminating agent and by avoiding excessively long reaction times.

The amines were readily separated from the non-basic by-products by extraction of a benzene solution of all organic matter with dilute hydrochloric acid. The desired amine boiled sufficiently lower than the higher amines to allow separation in fairly pure form by careful distillation of a basic extraction mixture. Further purification was readily accomplished by recrystallization of the hydrochlorides. In the present work a large excess of ammonia (or methylamine) was employed and only small amounts of the higher amines were formed.

Primary chlorides generally gave better yields than did secondary chlorides. This is in accord with the observations of Cheronis,[8] who studied the reaction rates of the four bromobutanes with alcoholic ammonia, and evaluated the yields therefrom.

The highest yields of amines were obtained from compounds having no substituent on the benzene ring. Moreover, the more labile the substituent, the lower was the yield. Thus fluoro derivatives gave better yields than did chloro derivatives, which in turn were more productive than bromo compounds. Yields were markedly lower in the amination of *ortho* substituted arylchloropropanes than in the case of *para* isomers.

Experimental

1-Aryl-2-chloropropanes.—The procedure for preparation of 2-chloro-1-(*o*-chlorophenyl)-propane and 2-chloro-1-(*p*-chlorophenyl)-propane is given as typical for this class of compounds. A mixture of 450 g. (4.0 moles) of chlorobenzene and 32.4 g. (0.2 mole) of anhydrous ferric chloride was cooled to −21° by an ice–salt-bath. Allyl chloride (76.5 g., 1.0 mole) was then added dropwise with stirring over a two-hour period. Stirring was continued for three hours longer. Meanwhile the temperature had risen to −16°. Hydrogen chloride was evolved weakly throughout the entire reaction period. The mixture was shaken

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(3) Abel, *Z. physiol. Chem.*, **28**, 318 (1899); *Chem. Zentr.*, **60**, II, 882 (1889).

(4) Barger and Dale, *J. Physiol.*, **41**, 19 (1910).

(5) Nenitzescu and Isacescu, *Ber.*, **66**, 1100 (1933).

(6) Truffault, *Bull. soc. chim.*, **6**, 726 (1939); *Compt. rend.*, **202**, 1286 (1936); **207**, 676 (1938).

(7) Clark, Olin and Deibel, U. S. Patent 2,183,499 (Dec. 12, 1939).

(8) Cheronis, *Trans. Illinois State Acad. Sci.*, **31**, 126 (1938); *C. A.*, **33**, 6792 (1939).

TABLE I

ARYLCHLOROPROPANES FROM ALLYL CHLORIDE

Compound	Yield, %	B. p., °C.	Mm.	d^{20}_{20}	$n^{20}D$	Analyses, % Calcd.	Found
2-Chloro-1-(*p*-chlorophenyl)-propane	21	111–112	10	1.1678	1.5360	Cl 37.5	37.0
2-Chloro-1-(*o*-chlorophenyl)-propane	32	103	10	1.1706	1.5351	Cl 37.5	37.5
1-(*p*-Bromophenyl)-2-chloropropane	13	124–126	10	1.4100	1.5582	C 46.3	46.4
						H 4.3	4.1
1-(*o*-Bromophenyl)-2-chloropropane	31	115–117	10	1.4159	1.5568	C 46.3	46.2
						H 4.3	4.0
2-Chloro-1-(*p*-fluorophenyl)-propane	24	81	10	1.1186	1.4971	Cl 20.5	20.7
						F 11.0	11.0
2-Chloro-1-(*p*-methoxyphenyl)-propane	14	107	5	1.0891	1.5270	Cl 19.2	19.4
2-Chloro-1-phenylpropane	32	80–81[a]	10				
1-Chloro-2-phenylpropane	20	82–83[b]	10				
1-Chloro-2-(*p*-chlorophenyl)-propane	6	94[c]	5				

[a] Nenitzescu and Isacescu[5] reported 79° at 10 mm. [b] Truffault[6] reported 85° at 13 mm. [c] Truffault[6] reported 117° at 16 mm.

with about 1 kg. of crushed ice and 100 ml. of concentrated hydrochloric acid. The organic layer was separated and washed with dilute hydrochloric acid, and finally with distilled water. It was then filtered to remove a small amount of solid condensation product, and dried over anhydrous calcium sulfate.

The dried reaction mixture was distilled from a Claisen flask to effect a rough separation of unreacted materials, product, and tar. The fraction containing the products was carefully rectified at 10 mm. pressure, using a 5-foot, glass-helices-packed column. A reflux ratio of 25:1 was maintained. Two products, boiling at 103° at 10 mm. and 111–112° at 10 mm., respectively, were obtained from the rectification. They yielded *o*-chlorobenzoic acid and *p*-chlorobenzoic acid, respectively, on permanganate oxidation. From the rectification curve and density data the yields were calculated to be 32% of 2-chloro-1-(*o*-chlorophenyl)-propane and 21% of 2-chloro-1-(*p*-chlorophenyl)-propane, or a total yield of 53% of products.

No allyl chloride was recovered from the reaction; however, rectification of the lower boiling fraction from the first distillation yielded, in addition to chlorobenzene, two compounds whose boiling points corresponded to 1,2-dichloropropane (9 g.) and 1,3-dichloropropane (12 g.). No attempt was made to prove their identity conclusively. Further distillation of the tarry residue from the reaction produced a viscous, slightly fluorescent oil (b. p. 133–135° at 2 mm.), consisting of bis-(chlorophenyl)-propanes (10–12% yield). The remainder of the material was non-distillable tar.

TABLE II

AMINES BY AMMONOLYSIS OF CHLORIDES

Compound, propylamine	Yield, %	B. p., °C.	Mm.	M. p. of derivative, °C.	d^{20}_{20}	$n^{20}D$	Analyses, % Calcd.	Found
2-(*p*-Chlorophenyl)-1-	40	99–101	5	205[a]	0.9639	1.5398	C 45.2[a]	45.2
							H 3.8[a]	4.0
1-(*p*-Chlorophenyl)-2-	44	93–94	5	164–165[b]	1.0762	1.5343	C 63.7[c]	63.8
							H 7.1[c]	7.3
1-(*p*-Bromophenyl)-2-	35	123–124	10	204–206[b]	1.3080	1.5569	Ion. Cl 14.2[b]	14.2
1-(*o*-Bromophenyl)-2-	26	118	10	200–201[b]	1.2984	1.5582	Ion. Cl 14.2[b]	14.3
1-Phenyl-2-	51	80–82[d]	11	147–149[b,e]				
2-Phenyl-1-	51	81–83[f]	10	145[b]				
1-(*p*-Fluorophenyl)-2-	43	90[g]	15	152–154[b,h]				
1-(*o*-Chlorophenyl)-2-	25	103–105[i]	10	180[b,i]				
1-(*p*-Methoxyphenyl)-2-	20	105–106[k]	5	207–208[b,l]				
N-Methyl-2-phenyl-1-	62	95–96	15	155[a]	0.9178	1.5102	C 50.8[a]	51.0
							H 4.8[a]	4.8
N-Methyl-1-(*o*-chlorophenyl)-2-	24	110	10	156[a]	1.0536	1.5288	C 46.6[a]	46.5
							H 4.2[a]	4.4
N-Methyl-1-(*p*-chlorophenyl)-2-	35	114–115	10	103[a]	1.0442	1.5259	C 46.6[a]	44.4
							H 4.2[a]	4.6
N-Methyl-1-(*p*-fluorophenyl)-2-	41	87–89	10	125[a]	0.9984	1.4922	C 48.5[a]	48.7
							H 4.3[a]	4.3
N-Methyl-1-phenyl-2-	44	98–100[m]	20	133[b,n]				

[a] Picrate. [b] Hydrochloride. [c] Free amine. [d] Woodruff and Conger, THIS JOURNAL, **60**, 465 (1938), reported 102–104° at 22 mm. [e] Woodruff and Conger, *ibid.*, reported 152°. [f] v. Braun, Grabowski and Kirschbaum, *Ber.*, **46**, 1280 (1913), reported 104° at 21 mm. [g] Suter and Weston, THIS JOURNAL, **63**, 602 (1941), reported 95–96° at 17 mm. [h] Suter and Weston, *ibid.*, reported 156–157°. [i] Johns and Burch, THIS JOURNAL, **60**, 919 (1938), reported 75–80° at 8 mm. [j] Johns and Burch, *ibid.*, reported 175–176°. [k] Mannich and Jacobsohn, *Ber.*, **43**, 189 (1910), reported 158° at 25 mm. [l] Mannich and Jacobsohn, *ibid.*, reported 210°. [m] Woodruff, Lambooy and Burt, THIS JOURNAL, **62**, 922 (1940), reported 78–80° at 6 mm. [n] Woodruff, Lambooy and Burt, *ibid.*, reported 135–136°.

Other 1-aryl-2-chloropropanes, listed in Table I, were prepared similarly using bromobenzene, fluorobenzene, and anisole in place of chlorobenzene.

1-Chloro-2-(*p*-chlorophenyl)-propane.—The method was adapted from Truffault.[6] To a mixture of 380 g. (*ca.* 4.0 moles) of fuming sulfuric acid (10% oleum) and 337.5 g. (3.0 moles) of chlorobenzene there was added over a two-hour period with stirring and cooling, 153.0 g. (2.0 moles) of allyl chloride. The mixture was stirred overnight at room temperature. The reaction mixture was shaken with several times its volume of crushed ice, washed with water and dried over anhydrous calcium sulfate. The dried product was rectified to strip off lower boiling components. A higher fraction, boiling at 91–99° at 6 mm., was refractionated at 5 mm. pressure. Two distinct materials, boiling at 90.5–92.0° at 5 mm. and 94.0° at 5 mm., respectively, were obtained. The latter compound gave a negative test for active chlorine with alcoholic silver nitrate in the cold. Permanganate oxidation yielded *p*-chlorobenzoic acid, proving that it was 1-chloro-2-(*p*-chlorophenyl)-propane (reported by Truffault). The yield was 6%. The former compound, evidently an isomer (d^{20}_{20} 1.1801, $n^{20}D$ 1.5404, calculated for $C_9H_{10}Cl_2$, 37.5% Cl, found, 37.4% Cl), was not identified conclusively. It gave a positive test for active chlorine with alcoholic silver nitrate, but failed to yield a solid acid derivative on treatment with permanganate, dichromate, or nitric acid-silver nitrate. It was obtained in 7.5% yield.

Ammonolysis of Chloro Compounds to Primary Amines.—The preparation of benzedrine is typical of the method used for synthesis of the primary amines listed in Table II. Twenty-five grams (0.16 mole) of 2-chloro-1-phenylpropane was dissolved in 450 ml. of saturated alcoholic ammonia solution (125 g./l.) and sealed in an iron-pipe autoclave. The autoclave was mechanically rocked and was heated by an electric resistance winding. The charge was heated at about 160° for nine hours. It was then allowed to cool and filtered. The alcohol and excess ammonia were distilled, and the residue was made strongly basic with 6 *M* sodium hydroxide. The basic mixture was extracted four to five times with 20-ml. portions of benzene, and the aqueous residue was discarded. The benzene solution was next extracted three to four times with 15-ml. portions of 6 *M* hydrochloric acid to secure the amine as a solution of its hydrochloride. The aqueous acid solution was made basic with sodium hydroxide and extracted several times with benzene. The latter benzene solution was dried over anhydrous potassium carbonate. This benzene solution was distilled from a Claisen flask giving 11.1 g. of benzedrine boiling at 80–82° at 11 mm. The yield was 51%.

Ammonolysis of Chloro Compounds to Secondary Methylamines.—The technique for preparing the N-methylamines listed in Table II was identical to that used for synthesis of the primary amines, except that an alcoholic solution of methylamine (204 g. per liter) was used as the aminating agent.

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Summary

The reaction of allyl chloride and benzene in the presence of ferric chloride to produce 2-chloro-1-phenylpropane, described by Nenitzescu and Isacescu, has been extended to four other aromatic compounds. Total yields of arylchloropropanes were 14 to 53%.

Truffault's method of adding aromatic compounds to allyl chloride in the presence of sulfuric acid was utilized for the preparation of 2-aryl-1-chloropropanes.

Nine arylchloropropanes have been treated with alcoholic ammonia to give 20–51% yields of the corresponding arylpropylamines. Five of the arylchloropropanes yielded 24–62% of the N-methylarylpropylamines on treatment with alcoholic methylamine.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

A Polymer Reaction Product of Tyrosine and Formaldehyde

BY ALFRED E. BROWN[2]

In a study of modified proteins[3] it was found that when the free amino groups of the protein were apparently completely acylated, the derivatives still had an appreciable formaldehyde-combining capacity as determined by a modification of the method of Nitschmann, *et al.*,[4] which involves acid hydrolysis of the formaldehyde-treated products, and distillation and titration of the formaldehyde. In addition to the acid-labile formaldehyde, it may well be that linkages stable to acid hydrolysis can be formed by proteins and formaldehyde.[5] The possibility that the 1(−)-tyrosine[6] side chain is involved in binding formaldehyde has been mentioned.[7] We were interested, therefore, in investigating the manner in which the hydroxyphenyl group of tyrosine might react with formaldehyde as well as in the stability to acid hydrolysis of any linkages which might thus be formed. The reaction with tyrosine itself was first studied, with the expectation of subsequently using N-acylated tyrosine derivatives and peptides of tyrosine. It will be evident that the experimental conditions employed in the present work were different from those ordinarily used to harden proteins with formaldehyde.

Ullmann and Brittner[8] were able to prepare

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

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(3) Gordon, Brown and McGrory, *Ind. Eng. Chem.*, **38**, 90 (1946).

(4) Nitschmann, Hadorn and Lauener, *Helv. Chim. Acta*, **26**, 1069 (1943); Wood, Swain and Kokes, to be published.

(5) Baudouy, *Compt. rend.*, **214**, 692 (1942).

(6) l(-)-tyrosine was used throughout the investigation so the prefix l(-) will be omitted henceforth.

(7) Carpenter and Lovelace, *Ind. Eng. Chem.*, **36**, 680 (1944); Nitschmann and Hadorn, *Helv. Chim. Acta*, **27**, 299 (1944).

(8) Ullmann and Brittner, *Ber.*, **42**, 2539 (1909).