[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Condensation of Unsaturated Amines with Aromatic Compounds. The Preparation of β-Substituted Phenethylamines[1]

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In a previous paper,[3] physiologically active phenethylamines of the type $C_6H_5CHRCH(CH_3)NHR$ and $C_6H_5CR_2CH(CH_3)NHR$ were described. Following this study, an investigation of the simpler β-substituted and the β,β-disubstituted phenethylamines was undertaken. One amine of the first type, namely, β-methylphenethylamine, had been mentioned previously[4-7] and some preliminary pharmacology was given by Hartung[5] and Woodruff.[4] When part of this work had been completed, the N-methyl, N-ethyl, and a series of methoxyphenyl derivatives of this amine were reported by Woodruff and co-workers.[8] Later Hauschild[9] published some pharmacological data on the primary amine and the N-methyl and *p*-amino derivatives.

The published syntheses of the β-substituted amines leave much to be desired. The alkylation and reduction of benzyl cyanide results in poor yields[5] of the amine. Another procedure involves the Reformatsky reaction with the appropriate alkyl aryl ketone followed by reduction, formation of the amide, the Hofmann reaction and, for a secondary or tertiary amine, alkylation.[8] β,β-Dimethylphenethylamine has apparently not been prepared previously. The β-methyl-β-ethyl- and β,β-diethylphenethylamines have been obtained[10] in less than 5% yields by reduction of the amides. Sodium reduction of the cyanides gives chiefly the hydrocarbons.[10]

In a search for more convenient methods of obtaining these amines the condensation of allylamine and other unsaturated amines with benzene and several benzene derivatives has now been investigated. No previous reference to the behavior of unsaturated amines in this reaction has been found.

Attempts to condense allylamine with benzene in the presence of anhydrous hydrogen fluoride and boron fluoride under the conditions of our experiments gave at best no more than a trace of condensation product. No product was obtained when concentrated sulfuric acid was the condensing agent, but here the expected β-methylphenethylamine may have undergone nuclear sulfonation and been lost; this was not investigated however. In the presence of an excess of aluminum chloride the condensation occurred readily, the yield of practically pure β-methylphenethylamine amounting to 85–94% of the theoretical amount.

Allylamine was found to condense with fluorobenzene and with toluene to give products which were chiefly the para isomers as shown by oxidation to *p*-fluorobenzoic and terephthalic acids. No more than a trace of amine was formed in several experiments involving anisole and allylamine.

In extending the condensation reaction to secondary amines containing the allyl group considerable difficulty was encountered in preparing a suitable quantity of allylmethylamine. The reaction of allyl chloride with excess methylamine in alcohol gave little but diallylmethylamine, paralleling earlier experiments in which allyl bromide was employed.[11] From the nitrosation and then hydrolysis of allylmethylaniline[12] the yield of amine obtained was 23%. The yield of product from the reduction of *p*-toluenesulfonallylmethylamide, $p\text{-}C_7H_7SO_2N(CH_3)CH_2CH{=}CH_2$, with sodium and butyl alcohol was considerably higher (48%). Reduction with sodium also proceeded readily in liquid ammonia, but isolation of the amine was difficult.

Allylmethylamine reacted readily with benzene in the presence of aluminum chloride, but attempts to condense *p*-toluenesulfonallylmethylamide and benzene directly were not successful. The desired condensation reaction took place readily with the other secondary and tertiary amines derived from allylamine and also with

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(2) (a) Sharp and Dohme Research Associate, 1938–40; (b) Sharp and Dohme Research Associate, 1940-41.

(3) Suter and Weston, THIS JOURNAL, **64**, 533 (1942).

(4) Woodruff and Pierson, *ibid.*, **60**, 1076 (1938).

(5) Hartung and Munch, *ibid.*, **53**, 1879 (1931); Tainter, *Arch. intern. pharmacodynamie*, **46**, 205 (1933).

(6) von Braun, Grabowski and Kirschbaum, *Ber.*, **46**, 1208 (1913); Barger and Dale, *J. Physiol.*, **41**, 19 (1910–11).

(7) Freund and König, *Ber.*, **26**, 2875 (1893).

(8) Woodruff, Lambooy and Burt, THIS JOURNAL, **62**, 922 (1940).

(9) Hauschild, *Arch. exp. Path. Pharmakol.*, **195**, 647 (1940).

(10) Blondeau, *Ann. chim.*, [2] **10**, 5 (1924).

(11) Partheil and v. Broich, *Ber.*, **30**, 519 (1897).

(12) Zeile and Meyer, *Z. physiol. Chem.*, **256**, 131 (1938).

methallylamine and related compounds. The results are summarized in Table I.

The preparations of β-methylphenethylamine and its N-methyl derivatives were also accomplished by the action of ammonia and methylamine, respectively, upon β-methylphenethyl bromide. In these preparations two reactions occurred simultaneously: (1) the formation of the amine and (2) elimination of hydrogen bromide to give methylstyrene. The yield of the olefin was approximately twice that of the amine.

The toxicity data in the last three columns of Table II were obtained by oral administration of an aqueous solution of the hydrochloride salt to white mice[13] according to the procedure mentioned earlier.[14] The pressor activity of these compounds is under investigation.

TABLE I

AMINE CONDENSATIONS, ALUMINUM CHLORIDE CATALYST

Unsaturated amine	Arylethylamine[a]	Yield, %	B. p., °C. (mm.)	n^{20}_D	d^{20}_4	Analyses, %[e] Calcd. C	Calcd. H	Calcd. Neut. equiv.	Found C	Found H	Found Neut. equiv.
$CH_2{=}CHCH_2NH_2$	$C_6H_5CH(CH_3)CH_2NH_2$	85–94	97–98 (19)[b]	1.5255	0.9483	...	...	...	...	...	...
	p-$FC_6H_4CH(CH_3)CH_2NH_2$	59	105–106 (22)	1.5066	1.0480	70.56	7.89	153.2	70.89	7.87	153.3
	p-$CH_3C_6H_4CH(CH_3)CH_2NH_2$	90	116–117 (22)	1.5241	0.9417	80.48	10.13	149.2	[f]	...	148.5
$CH_2{=}CHCH_2NHCH_3$	$C_6H_5CH(CH_3)CH_2NHCH_3$	47	86–87 (10)[c]	1.5112	.9207	...	...	149.2	...	...	149.7
$CH_2{=}CHCH_2NHC_2H_5$	$C_6H_5CH(CH_3)CH_2NHC_2H_5$	77	93 (10)[d]	1.5032	.9073	...	...	163.3	...	...	163.2
$CH_2{=}CHCH_2NHC_4H_9$-n	$C_6H_5CH(CH_3)CH_2NHC_4H_9$-$n$	66	121–123 (12)	1.4950	.8950	81.60	11.07	191.3	81.20 81.57	10.91 11.22	191.1
$CH_2{=}CHCH_2N(CH_3)_2$	$C_6H_5CH(CH_3)CH_2N(CH_3)_2$	62	79–80 (10)	1.4983	.8942	80.91	10.50	163.3	81.11	10.11	163.1
$CH_2{=}CHCH_2N(C_4H_9$-$n)_2$	$C_6H_5CH(CH_3)CH_2N(C_4H_9$-$n)_2$	45	148–150 (12)	1.4858	.8759	82.51	11.82	247.4	[g]	...	248.2
$CH_2{=}C(CH_3)CH_2NH_2$	$C_6H_5C(CH_3)_2CH_2NH_2$	84	75–76 (5)	1.5238	.9495	80.48	10.13	149.2	80.18 80.34	10.55 10.62	149.2
$CH_2{=}C(CH_3)CH_2NHCH_3$	$C_6H_5C(CH_3)_2CH_2NHCH_3$	70	84–85 (9)	1.5101	.9216	80.91	10.50	163.3	81.01	10.20	163.4
$CH_2{=}C(CH_3)CH_2N(CH_3)_2$	$C_6H_5C(CH_3)_2CH_2N(CH_3)_2$	83	87–88 (10)	1.4997	.8992	81.28	10.80	177.3	81.49 81.41	10.29 10.17	177.7

[a] From condensation of the unsaturated amine with benzene except in the second and third experiments where fluorobenzene and toluene, respectively, were used. [b] B. p. 92° (12 mm.), ref. 4; b. p. 104° (21 mm.), ref. 6. [c] B. p. 96–98° (18 mm.), ref. 8. [d] B. p. 127° (30 mm.), ref. 8. [e] The purity of all amines was first determined by titration with standard acid. At the request of the reviewer carbon and hydrogen analyses were then made on new compounds. [f] Analyses of this compound gave erratic values which were about 2–3% low in carbon. This behavior has not been explained. [g] No sample available.

Experimental

Condensation of Allylamine with Benzene.—To a cold mixture (0°) of 80.1 g. (0.6 mole) of anhydrous aluminum chloride and 78 g. (1 mole) of benzene in a 200-ml. three-necked flask, fitted with a mercury-sealed stirrer, thermometer and a T-tube which carried a dropping funnel and served as a gas outlet, was added slowly 11.4 g. (0.2 mole) of allylamine in an equal volume of benzene. An exothermic reaction ensued and some hydrogen chloride was evolved. The reaction mixture was allowed to become warm by removal of the ice-bath and was then refluxed six hours. After standing overnight the mixture was hydrolyzed with ice, the benzene layer separated and the aqueous layer extracted once with ether to remove colored material. Excess 30% sodium hydroxide was added to the acid aqueous layer, the free amine separated, the aqueous layer extracted with ether and the combined amine solutions dried and distilled. The total yield of β-methylphenethylamine distilling at 97–100° (19 mm.) was 25.2 g. or 93.5% of the theoretical amount. Other condensations were carried out in a similar manner. The data are given in Table I. The amine hydrochlorides prepared in the usual manner are reported in Table II. When the catalyst was hydrogen fluoride, sulfuric acid, or boron trifluoride only a trace of condensation product was isolated.

Reaction of Ammonia and Methylamine with β-Methylphenethyl Bromide.—The β-methylphenethyl bromide was prepared from allyl bromide and benzene according to the procedure for preparing cyclohexylbenzene.[15] The yield was 40% for the fraction of b. p. 106–113° (15 mm.). Truffault[16] also reported this yield but his procedure was not given in detail. A higher constant boiling fraction [144° (13 mm.), $n^{20}D$ 1.5628] from the condensation was not a definite compound as it had a bromine content of 10%. An attempt to condense allyl bromide with benzene in the

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(13) We are grateful to Dr. Paul A. Mattis and Mr. Albert R. Latvin of Sharp and Dohme for permission to include a summary of their experiments on the toxicity of these compounds.

(14) Suter and Weston, THIS JOURNAL, **63**, 602 (1941).

(15) Corson and Ipatieff, "Organic Syntheses," **19**, 36 (1939).

(16) Truffault, *Bull. soc. chim.*, **6**, 726 (1939).

TABLE II

HYDROCHLORIDES OF β-SUBSTITUTED PHENETHYLAMINES

Amine	M. p., °C. HCl salt	Chlorine, % Calcd.	Chlorine, % Found	LD_0	LD_{50}	LD_{100}
$C_6H_5CH(CH_3)CH_2NH_2$	143 –144.5[a]	20.65	20.67	350	485	650
p-$FC_6H_4CH(CH_3)CH_2NH_2$	149 –150	18.70	18.69	350	500	700
p-$CH_3C_6H_4CH(CH_3)CH_2NH_2$	174 –176	19.11	19.16	300	375	450
$C_6H_4CH(CH_3)CH_2NHCH_3$	145 –145.5[b]	19.11	19.17	350	515	650
$C_6H_5CH(CH_3)CH_2NHC_2H_5$	158.5–159.5[c]	17.75	17.68	...	...	...
$C_6H_5CH(CH_3)CH_2NHC_4H_9$-$n$	154 –155.5	15.57	15.67	150	175	250
$C_6H_5CH(CH_3)CH_2N(CH_3)_2$	221 –222.5	17.75	17.70	...	...	...
$C_6H_5C(CH_3)_2CH_2NH_2$	200 –201.5	19.11	19.16	175	218	275
$C_6H_5C(CH_3)_2CH_2NHCH_3$	218.5–219.5	17.75	17.74	250	325	450
$C_6H_5C(CH_3)_2CH_2N(CH_3)_2$	199 –200	16.59	16.53	...	...	...

[a] Cryst. from ethyl acetate. M. p. 146–147°, ref. 4; m. p. 123–124°, ref. 5. [b] M. p. 148–159°, ref. 8. [c] M. p. 159–160°, ref. 8.

presence of boron fluoride at room temperature gave a yield of less than 1%.

By the reaction of 2 l. of absolute alcohol, saturated with ammonia at 7°, with 49.8 g. (0.25 mole) of β-methylphenethyl bromide in a tightly stoppered bottle at room temperature for ten days, there was obtained only an 8% yield of β-methylphenethylamine and 34 g. of the bromide was recovered. Heating 34 g. (0.17 mole) of the bromide with 50 ml. of alcohol and 13 g. (0.93 mole) of ammonia in a 300-ml. bomb at 80–90° for fifty-four hours gave 5.8 g., b. p. 65–66° (23 mm.), of α-methylstyrene.[17] From the acid-soluble fraction 7.4 g. of amine, b. p. 89–90° (15 mm.), $n^{20}D$ 1.5255, a 32% yield, was obtained.

To a mixture of 39 g. (1.25 mole) of methylamine and 50 g. of absolute alcohol at 5° was added 49.8 g. (0.25 mole) of the bromide and the whole allowed to stand at room temperature for eleven days in a pressure bottle. Removal of the alcohol and excess amine on the steam-bath was followed by the addition of aqueous alkali and extraction with ether. Finally by extraction of the ether layer with dilute acid there was obtained from evaporation of the ether 15 g. (51%) of α-methylstyrene and from the acid layer 11.9 g. (32%) of the N,β-dimethylphenethylamine, b. p. 94–96° (17 mm.).

Preparation of Allylmethylamine.—To 43.2 g. (0.77 mole) of powdered potassium hydroxide in a little ethanol was added 143 g. (0.77 mole) of p-toluenesulfonmethylamide. Then 85 g. (1.1 mole) of allyl chloride was added and the mixture began to reflux. When the reaction had slowed and most of the alkali had dissolved the mixture was refluxed on the steam-bath for six hours. After removal of the alcohol and excess allyl chloride by distillation, the viscous liquid remaining was decanted from the salt into a Claisen flask and distilled under reduced pressure. There was obtained 155 g. of a light yellow liquid, b. p. 190–193° (12 mm.), $n^{20}D$ 1.5340, an 89% yield of p-toluenesulfonallylmethylamide. This was reduced by several procedures, the most satisfactory of which is described.

To a boiling solution of 45 g. (0.2 mole) of the p-toluenesulfonallylmethylamide in 500 ml. of n-butyl alcohol was added gradually in small pieces 46 g. (2 atoms) of sodium. The top of the condenser was fitted with a tube leading to a flask of hydrochloric acid. The mixture was refluxed for an hour after the final addition of sodium. After cooling, water was added and the whole distilled into hydrochloric acid until the distillate came over practically neutral. The combined acid solutions were evaporated to dryness under reduced pressure, the residue treated with concentrated aqueous sodium hydroxide and the amine distilled out, b. p. 65°, $n^{20}D$ 1.4065. The yield was 6.7 or 48% of the theoretical amount. A b. p. of 64–66° has been reported.[18]

Preparation of Other Unsaturated Amines.—Allylethylamine was prepared by shaking 280 g. of 33% ethylamine with 76.5 g. of allyl chloride until reaction was complete. Drying and fractionation of the amines formed gave 36.5 g. (43%) of allylethylamine, b. p. 82–84°, $n^{20}D$ 1.4145 and d^{20}_{20} 0.7536. Previously[19] boiling points of 84° and 84–86° have been reported. There was also obtained 15.6 g. of diallylethylamine, b. p. 129–130°, $n^{20}D$ 1.4360, d^{20}_{20} 0.7817.

Anal. Calcd. for $C_8H_{15}N$: neut. equiv., 125.2. Found: neut. equiv., 125.1.

Allyl-n-butylamine and allyl-di-n-butylamine were prepared by the method of Adams and co-workers.[20]

Allyldimethylamine, b. p. 61–64°, $n^{20}D$ 1.3998, was obtained in about 30% yield by shaking 50 g. (0.63 mole) of dimethylamine hydrochloride, 38.3 g. (0.5 mole) of allyl chloride, 30 g. (0.75 mole) of sodium hydroxide and 100 ml. of water in a pressure bottle until the fairly rapid reaction was complete. A b. p. of 64° has been reported by Knorr and Roth.[21]

β-Methylallylamine was prepared in about 20% yield by the action of methallyl chloride with ammonia (6 molecular equivalents) in aqueous alcohol. Previously[22] it had been obtained by other methods.

β-Methylallylmethylamine and β-methylallyldimethylamine, which are apparently new compounds, were also made from methallyl chloride. From 100 g. of 33% methylamine solution, 45.3 g. (0.5 mole) of methallyl chloride and 100 ml. of 95% alcohol after shaking and warming in a pressure bottle until reaction was complete there was

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(17) Auwers and Eisenlohr, *J. prakt. Chem.*, [2] **82**, 89 (1910).

(18) Zeile and Meyer, *Z. physiol. Chem.*, **256**, 131 (1938).

(19) Rinne, *Ann.*, **168**, 262 (1873); Liebermann and Paal, *Ber.*, **16**, 526 (1883).

(20) Burnett, Jenkins, Peet, Dreger and Adams, THIS JOURNAL, **59**, 2248 (1937).

(21) Knorr and Roth, *Ber.*, **39**, 1427 (1906).

(22) Adams and Cairns, THIS JOURNAL, **61**, 2464 (1939).

obtained 6.3 g. (15%) of β-methylallylmethylamine, b. p. 86–86.5° and n^{20}_{D} 1.4200 which was condensed with benzene after a titration indicated it was substantially pure.

Anal. Calcd. for $C_5H_{11}N$: neut. equiv., 85.15. Found: neut. equiv., 85.46.

There was obtained as the principal product 27.2 g. of di-(β-methylallyl)-methylamine, b. p. 145–145.5°, n^{20}_{D} 1.4372, which is 78% of the theoretical yield.

Anal. Calcd. for $C_9H_{17}N$: neut. equiv., 139.2; C, 77.63; H, 12.31. Found: neut. equiv., 141.1; C, 78.12; H, 11.95.

β-Methylallyldimethylamine, b. p. 82.4–82.6° (750 mm.), n^{20}_{D} 1.4092, was obtained in a 41% yield from dimethylamine and methallyl chloride.

Anal. Calcd. for $C_6H_{13}N$: neut. equiv., 99.2; C, 72.66; H, 13.21. Found: neut. equiv., 99.7; C, 73.06; H, 12.99.

The attempt to prepare unsaturated amines from the equilibrium mixture of crotyl chloride and 3-chloro-1-butene gave a complex mixture which has not been separated.

Oxidation Reactions.—The structures of the fluorobenzene and toluene condensation products were determined by oxidation with permanganate.[23] Terephthalic acid from the toluene derivative was identified as its dimethyl ester, m. p. 137–138°. No phthalic acid was isolated although the amine hydrochloride before purification melted over a range indicating the presence of more than one base. The crude *p*-fluorobenzoic acid also melted over a wide range but only the one acid was isolated.

Summary

1. A new method of preparing β-substituted phenethylamines by condensing unsaturated amines with aromatic compounds in the presence of aluminum chloride is described.

2. A number of allylamine derivatives have been prepared.

3. Some preliminary pharmacological data on the phenethylamines are reported.

[23] We are indebted to Mr. Kermit Streeter now of Sharp and Dohme for the oxidation experiments.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

Anthochlor Pigments. IV. The Pigments of *Coreopsis grandiflora*, Nutt. I.

BY T. A. GEISSMAN AND CHARLES D. HEATON

In the continuation of studies on the flower pigments of those members of the tribe *Heliantheae*, family *Compositae*, which contain pigments of the anthochlor type, the examination of the flowers of *Coreopsis grandiflora*, Nutt. has been undertaken. Previous work has shown that the tetrahydroxychalcone butein (I) is present in *Dahlia variabilis* (yellow),[1] *Coreopsis Douglasii*[2] and *Coreopsis gigantea*,[3] and that a butein glycoside, coreopsin, is present in *Cosmos Sulphureus*[4] and *Coreopsis gigantea*.[3]

Coreopsis grandiflora, Nutt. is a common garden perennial whose showy orange-yellow rays and yellow disk-florets show the presence of pigments of the anthochlor type by their color change to deep red when treated with dilute alkali. Since the formation of orange to red salts with alkali is a characteristic property of many polyhydroxy chalcones, particularly those containing the 3,4-dihydroxyphenyl residue as ring B (*cf.* XIII), it has heretofore appeared reasonable to expect that the anthochlor pigments would all prove to be substances of this type. An interesting and from the standpoint of the biosynthetical aspects of pigment formation, important departure from this expectation is encountered in the case of *Coreopsis grandiflora*. From the ray flowers of this species have been isolated four compounds. One of these is the known flavone, luteolin (II), which has been reported to occur in *Cosmos Sulphureus*.[4] The other three compounds are new. One of them is a flavanone (III) which is probably 8-methoxybutin; this may occur in the flower as the chalcone, 3′-methoxybutein, and may have been isomerized to the flavanone in the isolation process, but no evidence on this point is available at present. The remaining two compounds are related as glucoside and aglucone. The aglucone gives the typical anthochlor color change with alkali but it is not a polyhydroxychalcone. It appears from present evidence to be unique in that it is probably a polyhydroxybenzalcoumaranone, and as such is probably the first representative of this structural type to be isolated from a natural source.[5] These substances will be re-

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[1] Price, *J. Chem. Soc.*, 1018 (1939).

[2] Geissman, THIS JOURNAL, **63**, 656 (1941).

[3] Geissman, *ibid.*, **63**, 2689 (1941).

[4] Geissman, *ibid.*, **64**, 1704 (1942).

[5] The structures of pedicinin and isopedicin, which were originally considered to be methyl ethers of a tetrahydroxybenzalcoumaranone [Sharma and Siddiqui, *J. Indian Chem. Soc.*, **16**, 1 (1939)] are still not established, and Bose and Dutt [*J. Indian Chem. Soc.*, **17**, 499 (1940)] have assigned to them a structure containing a cinnamoylbenzoquinone nucleus.