[Contribution from the Chemical Laboratories of the University of Maryland]

SYNTHESES OF SOME PHENETHYL AND PHENBUTYL AMINES

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The earlier work (1) on synthetic analgesics in this laboratory had indicated the desirability of preparing a series of amines with structural variations as shown in Figure 1.

This paper is concerned with syntheses of amines in which *n* has the value of 1 and 3; substances wherein *n* had the value of 2 have been reported elsewhere (2). Some further members of the phenethylamines ($n = 1$), have been prepared as shown in Table I. Generally these compounds were prepared by the alkylation of phenylacetonitrile with sodamide in ether, conversion of the nitrile to the amide, and reduction of the amide with lithium aluminum hydride to the amine. The amines were usually isolated as the hydrochlorides following the reduction with lithium aluminum hydride and were recrystallized from ethyl ether-abs. ethanol. This process was used instead of direct reduction of the nitrile to amine in order to have an additional stage for purification. The nitriles are given in Table II and the amides in Table III. Some of these amines were then submitted to substitution in the aromatic nucleus, and the amino group was methylated (3) using formic acid and formaldehyde, as for instance substances II, III, etc. of Table I. Nitration in the aromatic nucleus was accomplished by the potassium nitrate-sulfuric acid method and the nitro group was reduced catalytically. Compound XV was prepared by the diazotization of the aromatic amino group of XIV, and subsequent replacement of the diazonium chloride with the hydroxyl group in the standard manner. Compound XX was obtained from the alkylation product of α-phenylpropionitrile using sodamide with 1-diethylamino-3-bromopropane and conversion to the diamine as indicated above.

Several amines wherein *n* of the original formula has the value of 3 were prepared and are shown in Table IV. The synthesis involved consisted of the following steps: condensation of mesityl oxide with benzene; the ketonic product was subjected to the Willgerodt reaction (Kindler Modification); conversion of the acid to the acid chloride; reaction of the acid chloride with ammonia or methylamine; and reduction with lithium aluminum hydride. Compound XXVII was obtained by the alkylation of XXV. The acid from the Willgerodt reaction, $C_6H_5C(CH_3)_2CH_2CH_2COOH$, was cyclized with sulfuric acid to yield 4,4-dimethyl-1-tetralone. The tetralone was converted to compound XXVIII *via* catalytic reduction of the oxime.

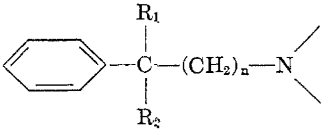
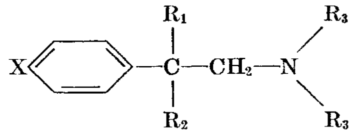


Fig. 1

TABLE 1

PHENETHYL AMINES

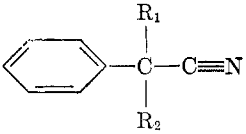


No.	X	R₁	R₂	R₃	n_D^t	B.P., °C.	mm.	Base, Analyses				Hydrochloride Analyses				
								Calc'd		Found		Calc'd		Found		m.p., °C.
								C	H	C	H	C	H	C	H	
I	H	CH_3	C_2H_5	H	1.520^{25}	103	9	80.90	10.50	80.33	10.45	66.13	9.08	66.00	9.00	189–190
II	NO_2	CH_3	C_2H_5	H	1.548^{30}	105	0.5	63.43	7.74	63.90	7.81	53.98	7.00	53.68	7.00	184–186
III	NO_2	CH_3	C_2H_5	CH_3		112	0.4	66.07	8.53	66.33	8.64	57.20	7.76	57.54	7.86	218–220
IV	NH_2	CH_3	C_2H_5	H	1.563^{30}	120	0.7	74.10	10.17	73.97	10.18					193–194
V	NH_2	CH_3	C_2H_5	CH_3	1.536^{30}	92	0.1	75.67	10.75	75.62	10.81	55.91	8.66	55.71	8.65	250–255
VI	H	CH_3	$n\text{-}C_3H_7$	H	1.515^{24}	75–80	1.5	81.39	10.81	81.65	10.74	67.43	9.48	67.83	9.31	146–148
VII	NO_2	CH_3	$n\text{-}C_3H_7$	H		145–155	1.5					55.70	7.40	55.49	7.25	184–188
VIII	NH_2	CH_3	$n\text{-}C_3H_7$	H	1.557^{24}	145–150	2.8					54.34	8.36	54.66	8.28	206–209
IX	H	C_2H_5	$n\text{-}C_3H_7$	H	1.517^{26}	82–85	0.8	81.61	11.07	81.74	11.04	68.54	9.74	68.83	9.71	155–160
X	H	C_2H_5	$n\text{-}C_3H_7$	CH_3	1.502^{26}	73–77	0.5	82.13	11.49	82.35	11.27	70.42	10.25	70.65	10.03	184–187
XI	NO_2	C_2H_5	$n\text{-}C_3H_7$	H		135–140	0.3					57.23	7.76	57.06	7.87	206–208
XII	NH_2	C_2H_5	$n\text{-}C_3H_7$	H		125–130	0.9			mono (HCl)		64.31	9.55	63.99	9.49	135–138
										di (HCl)		55.91	8.61	55.61	8.57	234–238
XIII	NO_2	C_2H_5	$n\text{-}C_3H_7$	CH_3		123–127	0.1					59.88	8.38	59.86	8.32	193–196
XIV	NH_2	C_2H_5	$n\text{-}C_3H_7$	CH_3		135–140	1.5					58.62	9.18	58.50	9.53	160–163
XV	OH	C_2H_5	$n\text{-}C_3H_7$	CH_3		[a]		76.54	10.71	76.13	10.51	66.27	9.64	66.31	9.38	138–140
XVI	H	$n\text{-}C_3H_7$	$n\text{-}C_5H_{11}$	H	1.506^{26}	110–112	0.9	82.33	11.66	82.41	11.52	71.21	10.46	71.28	10.70	88–92
XVII	NO_2	$n\text{-}C_3H_7$	$n\text{-}C_5H_{11}$	H		175–185	0.9					61.03	8.65	61.11	8.52	159–161
XVIII	NH_2	$n\text{-}C_3H_7$	$n\text{-}C_5H_{11}$	H								59.80	9.41	59.10	9.02	183–187
XIX	H	$n\text{-}C_3H_7$	$n\text{-}C_5H_{11}$	CH_3	1.496^{26}	117–119	2	82.69	11.95	82.51	11.75	72.57	10.83	72.58	10.79	132–136
XX	H	CH_3	$CH_2CH_2CH_2(C_2H_5)_2N$	H	1.509^{26}	128–132	2	77.36	11.36	77.37	11.33					
XXI	H	C_2H_5	C_2H_5	H								67.42	9.43	67.61	9.67	181–184
XXII	H	C_2H_5	C_2H_5	CH_3								69.53	10.00	69.46	10.13	220–225
XXIII	NO_2	C_2H_5	C_2H_5	CH_3								58.63	8.12	58.48	8.13	218–220
XXIV	NH_2	C_2H_5	C_2H_5	CH_3								57.33	8.97	57.39	9.02	250–252

[a] M.p. 99–102°.

TABLE II

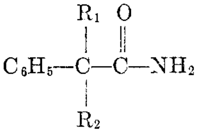
PHENYLACETONITRILES



R_1	R_2	B.P., °C.	mm.	n_D^t	Analyses				Yield, %
					C		H		
					Calc'd	Found	Calc'd	Found	
CH_3	n-C_3H_7	135–145	2.3	1.5028^{24}	83.18	82.93	8.73	8.96	75
C_2H_5	n-C_3H_7	98–102	4.5	1.5001^{24}	83.37	83.46	9.15	9.12	63.6
n-C_3H_7	n-C_5H_{11}	105–115	0.2	1.4959^{25}	83.78	83.93	10.11	9.97	70
CH_3	$(CH_2)_3N(C_2H_5)_2$	117–119	0.5	1.4981^{25}	78.63	78.83	9.90	9.75	47

TABLE III

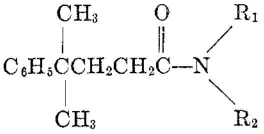
A. PHENYLACETAMIDES



$C_6H_5—C(R_1)(R_2)—C(=O)—NH_2$

R_1	R_2	M.P., °C.	B.P., °C.	mm.	Analyses				Yield, %
					Calc'd		Found		
					C	H	C	H	
CH_3	C_2H_5	75			74.52	8.53	74.65	8.58	45
CH_3	n-C_3H_7	—	125–145	1.5	75.35	8.96	77.29	8.99	37
C_2H_5	n-C_3H_7	—	122–125	1.0	76.05	9.34	77.19	9.54	46
n-C_3H_7	n-C_5H_{11}	81–83	—		77.68	10.19	78.42	9.95	—
C_2H_5	C_2H_5	43–44	—		75.35	8.95	73.13	9.09	

B. PHENYLBUTYRAMIDES



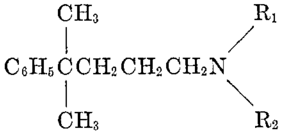
$C_6H_5C(CH_3)_2CH_2CH_2C(=O)—N(R_1)(R_2)$

R_1	R_2	M.P., °C.	B.P., °C.	mm.	Calc'd C	Calc'd H	Found C	Found H	Yield, %
H	H		151–154	0.9	75.35	8.96	75.43	9.03	71
H	CH_3		132–134	1.3	76.05	9.33	75.94	9.31	60
CH_3	CH_3	69–70			76.66	9.65	76.75	9.72	65

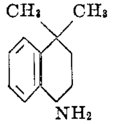
The condensation of ethyl chloroacetate with α-phenylpropionitrile provided the starting material XXIX for another series of substances which were important to this study (Fig. 2). The solid amino-alcohol XXX was readily obtained by reduction of the nitrile ester with lithium aluminum hydride. The ester nitrile XXIX was also used to prepare the pyrrolidines XXXIV and XXXVII. These substances can be considered as both phenethyl and phenpropyl amines—

TABLE IV

PHENBUTYLAMINES



$C_6H_5C(CH_3)_2CH_2CH_2CH_2NR_1R_2$

No.	R_1	R_2	B.P., °C.	mm.	Base Analyses				Hydrochloride Analyses				
					Calc'd		Found		Calc'd		Found		M.P., °C.
					C	H	C	H	C	H	C	H	
XXV	H	H	83-85	1.2	81.29	10.80	81.28	10.90	67.42	9.43	67.48	9.13	172-173
XXVI	H	CH_3	68-70	0.1	81.61	11.07	81.61	11.08	68.55	9.74	68.58	9.62	110-111
XXVII	CH_3	CH_3	73-75	0.7	81.89	11.29	81.84	11.16	69.54	10.00	69.80	10.27	150-151
XXVIII			(A)						68.07	8.57	67.73	8.53	233-234

(A) Derived from the cyclization of $C_6H_5C(CH_3)_2CH_2CH_2COOH$ with sulfuric acid. Yield: 45%; b.p. 93-94°/1.5 mm. (*Anal.* Calc'd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.74; H, 8.36.). *2,4-Di-nitrophenylhydrazone:* m.p. 229-230° (*Anal.* Calc'd for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.12. Found: C, 61.08; H, 5.10.). *Oxime,* m.p. 107-108° (*Anal.* Calc'd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99. Found: C, 76.27; H, 8.04.). The oxime was reduced catalytically in the usual manner to yield the amine.

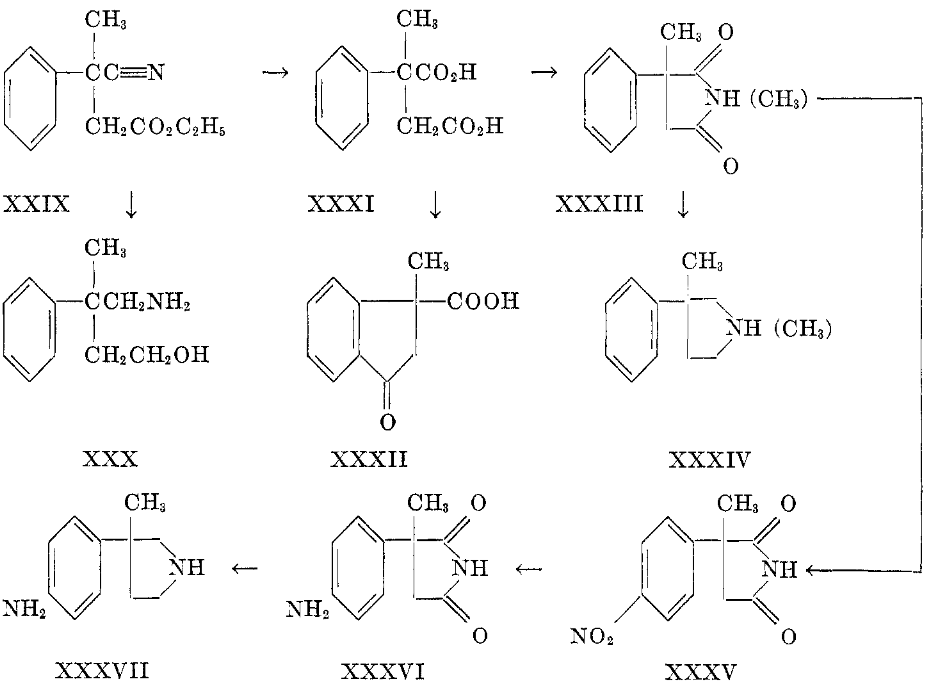


FIG. 2

incidentally they have a certain relationship to Demerol. The succinic acid XXXI was obtained by hydrolysis of XXIX and was cyclized to the carboxylic indanone XXXII *via* the acid chloride and aluminum chloride. This substance was not studied further. The imides XXXIII were obtained by heating the ammonium or methylammonium salts of XXXI. Reduction of the imides with lithium aluminum hydride provided the pyrollidines (XXXIV). Attempts to nitrate these pyrrolidines were unsuccessful and instead, to obtain XXXVII, nitration of α-methyl-α-phenylsuccinimide afforded the nitrophenylmethylsuccinimide (XXXV), which was readily reduced catalytically to XXXVI. This substance was soluble in water and quite insoluble in ether. The reduction of this material with lithium aluminum hydride could not be accomplished in the usual manner because of this limited solubility, but it was accomplished by means of the Soxhlet extraction procedure.

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EXPERIMENTAL

Ethyl 3-cyano-3-phenylbutyrate (XXIX). α-Phenylpropionitrile (131 g., 1.0 mole) was slowly added to a suspension of sodamide (42 g., 1.1 moles) in 1 liter of anhydrous ether. After the addition the mixture was stirred for 1 hour and ethyl chloroacetate (154 g., 1.1 moles) was added. When the reaction was complete, the mixture was poured into water and the organic layer was removed. The aqueous portion was extracted with ether and was added to the original organic layer which was then washed with water. The organic layer was dried over magnesium sulfate and the ether was removed. Distillation of the residue with vigorous heating yielded 47 g. (23%) of ethyl 3-cyano-3-phenylbutyrate boiling at 140–170°/0.2 mm. (By virtue of the very rapid distillation this boiling range and pressure are without much significance). Redistillation gave an analytical sample boiling at 113°/0.3 mm.

Anal. Calc'd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96.
Found: C, 71.97; H, 7.06.

3-Methyl-3-phenyl-4-aminobutan-1-ol (XXX). Ethyl 3-cyano-3-phenylbutyrate was reduced almost quantitatively with lithium aluminum hydride in ether. The product melted at 86° after several recrystallizations from a benzene-petroleum ether (30–40°) mixture.

Anal. Calc'd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56.
Found: C, 73.40; H, 9.56.

α-Methyl-α-phenylsuccinic acid (XXXI). Ethyl 3-cyano-3-phenylbutyrate (20 g.) was heated under reflux conditions for 5 hours with concentrated hydrochloric acid (100 ml.). On cooling a white solid separated which was isolated and recrystallized from glacial acetic acid. The product (95% yield) melted at 158°.

Anal. Calc'd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81.
Found: C, 63.88; H, 6.01.

3-Carboxy-3-methylindanone-1 (XXXII). α-Methyl-α-phenylsuccinic acid (10 g.) was heated under reflux conditions with 10 ml. of thionyl chloride. After 30 minutes the excess thionyl chloride was removed and 20 ml. of dry nitrobenzene was added. Anhydrous aluminum chloride (10 g.) was added in portions over a 30 minute period. When the addition was complete the mixture was heated to 90–95° for 1.5 hours, poured into water, and steam-distilled to remove the nitrobenzene. The residue from the steam-distillation was cooled and extracted with ether. The organic solution was extracted with dilute sodium hydroxide which was later acidified with hydrochloric acid. A solid separated which was recrystallized from benzene-petroleum ether (30–60°) and melted at 119°.

Anal. Calc'd for $C_{11}H_{10}O_3$: C, 69.47; H, 5.30.
Found: C, 69.13; H, 5.10.

α-Methyl-α-phenylsuccinimide (XXXIII). α-Methyl-α-phenylsuccinic acid was dissolved in an excess of concentrated ammonium hydroxide and the whole was submitted to distillation. Heating was continued so long as any distillate was obtained. The product distilling above 150° was collected and recrystallized from absolute alcohol. The once recrystallized imide melted at 63–65°.

3-Methyl-3-phenylpyrrolidine (XXXIV). α-Methyl-α-phenylsuccinimide was reduced with lithium aluminum hydride in ether. The product was isolated as the hydrochloride which melted at 133° after recrystallization from an ethanol-ether mixture.

Anal. Calc'd for $C_{11}H_{16}ClN$: C, 66.82; H, 8.16.
Found: C, 67.16; H, 8.01.

N-Methyl-3-methyl-3-phenylpyrrolidine (XXXIV) was prepared as the preceding compound, except that a 20% methylamine solution was substituted for the concentrated ammonium hydroxide. The poor analysis for the hydrochloride is attributed to its extreme hygroscopic nature.

Anal. Calc'd for $C_{12}H_{18}ClN$: C, 68.07; H, 8.57.
Found: C, 65.78; H, 8.46.

α-Methyl-α-(p-nitrophenyl)succinimide (XXXV). α-Methyl-α-phenylsuccinimide was nitrated using sulfuric acid as solvent and potassium nitrate (10% excess). The product melted at 156° after several recrystallizations from ethanol.

Anal. Calc'd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30.
Found: C, 56.65; H, 4.18.

α-(p-Aminophenyl)-α-methylsuccinimide (XXXVI). α-Methyl-α-(*p*-nitrophenyl)succinimide was reduced at room temperature with 10% palladinized charcoal. The pressure of hydrogen was slightly above atmospheric pressure. The amine melted at 166° after recrystallization from ethanol. The hydrochloride melted at 219°.

Anal. Calc'd for $C_{11}H_{13}ClN_2O_2$: C, 54.89; H, 5.44.
Found: C, 54.79; H, 5.36.

3-(p-Aminophenyl)-3-methylpyrrolidine (XXXVII). α-(*p*-Aminophenyl)-α-methylsuccinimide (5.2 g.) was placed in a porous thimble in a small Soxhlet extraction apparatus. A suspension of 9.5 g. of lithium aluminum hydride in 500 ml. of anhydrous ether was placed in the boiling flask which was heated so that a slow extraction of the amino-imide occurred. The extraction process was allowed to continue for 48 hours. The ethereal solution was decomposed with water and filtered. The ether layer was dried with magnesium sulfate, cooled, and a stream of dry hydrogen chloride was run into the solution. The solid which separated was recrystallized from ethanol and melted at 214°. The analysis corresponded to the monohydrochloride.

Anal. Calc'd for $C_{11}H_{17}ClN_2$: C, 62.10; H, 8.06.
Found: C, 62.03; H, 7.91.

SUMMARY

A number of phenethylamines and phenbutylamines have been prepared.

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REFERENCES

(1) SCHWARTZMAN AND WOODS, *J. Org. Chem.*, **17**, 492 (1952).
(2) WOODS, *et. al.*, *J. Org. Chem.*, **19**, 385 (1954).
(3) CLARKE, GILLESPIE, AND WEISSHAUS, *J. Am. Chem. Soc.*, **55**, 4571 (1933).