[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Antispasmodics. II. Substituted α-(β-Aminoethyl)-phenylacetonitriles and 3-Phenylpropylamines

BY A. WAYNE RUDDY[1]

In an attempt to find antispasmodics with greater musculotropic properties a number of substituted 3-phenylpropylamines have been prepared. These amines were obtained from the corresponding substituted aminoalkylphenylacetonitriles by treatment with sodium amide. Hydrochlorides and methiodides were prepared of the basic nitriles and the resulting 3-phenylpropylamines. The preliminary tests *in vitro* indicated that the most active compound against barium chloride induced spasms was N-(3-isobutyl-3-phenylpropyl)-piperidine.

In a previous paper[2] from these laboratories there was reported a number of substituted 3-phenylpropylamines which were found later to have principally a musculotropic type of activity. In an attempt to increase their musculotropic properties further study has been made in this series. Into the 3-position of the phenylpropylamines was introduced phenyl, cyclohexyl, cyclopentyl, *n*-hexyl, isobutyl, β-methallyl and isobutenyl groups. The various basic substituents were pyrrolidine, 2-methylpyrrolidine, dimethylamine, diethylamine and piperidine.

$$C_6H_5CRCN—CH_2—CH_2N\begin{matrix}R'\\R'\end{matrix} + 2NaNH_2 \longrightarrow$$

$$C_6H_5CHR—CH_2—CH_2—N\begin{matrix}R'\\R'\end{matrix} + NH_3 + Na_2N_2C$$

iently by stirring with sodium amide in refluxing benzene, but the aminoethylalkylphenylacetonitriles and cyclohexylphenylacetonitriles required the temperature of refluxing xylene for complete cleavage. The yields of amines from this reaction were very good with the exception of the β-methallyl and isobutenylphenylacetonitriles which gave 48 and 58%, respectively.

Four of the basic nitriles needed as intermediates, 4-dimethylamino-2,2-diphenylbutanenitrile,[4] 2,2-diphenyl-4-N-piperidylbutanenitrile,[5] 2,2-diphenyl-4-N-pyrrolidylbutanenitrile[4] and 4-diethylamino-2-*n*-hexyl-2-phenylbutanenitrile[6] have been prepared previously.

TABLE I

SUBSTITUTED α-(β-AMINOETHYL)-PHENYLACETONITRILES $C_6H_5—\underset{\displaystyle CN}{\overset{\displaystyle R}{\overset{|}{\underset{|}{C}}}}—CH_2—CH_2—Am$

		Base				Hydrochlorides and methiodides							
		Yield,	B.p.,			M.p., °C.		Nitrogen, %		Chlorine, %		Iodine, %	
R	Am	%	°C.	Mm.	$n^{25}D$	(cor.)	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found
Phenyl	NC_4H_8[a]	82	[b]			207-208.3	$C_{20}H_{22}N_2$.HCl	[c]		10.85	10.80		
						170.8-171.6	$C_{21}H_{25}IN_2$[d]	6.47	6.21			29.36	29.20
Phenyl	$NC_4H_7CH_3$[g]	78	[e]			[f]							
Cyclohexyl	$N(CH_3)_2$	72	150-158	1	1.5248	228.8-229.8	$C_{18}H_{26}N_2$.HCl	9.13	9.01	11.55	11.58		
						200-202	$C_{19}H_{29}IN_2$	6.79	6.52			30.78	30.65
Cyclohexyl	$N(C_2H_5)_2$	82	174-182	2	1.5188	156.8-158	$C_{20}H_{30}N_2$.HCl	8.37	8.36	10.59	10.60		
						168.8-169.6	$C_{21}H_{33}IN_2$	6.36	6.22			28.82	28.51
Cyclohexyl	NC_4H_8[a]	90	[e]			194.6-195.8	$C_{20}H_{28}N_2$.HCl	8.42	8.31	10.65	10.61		
Cyclohexyl	NC_5H_{10}[h]	82	[e]			230-232	$C_{21}H_{30}N_2$.HCl	8.08	8.12	10.22	9.96		
Cyclopentyl	$N(CH_3)_2$	73	134-140	1	1.5208	184-186	$C_{17}H_{24}N_2$.HCl	[i]		12.11	12.08		
n-Hexyl	$N(C_2H_5)_2$	70	138-142	0.2[j]	1.4937	103-105	$C_{20}H_{32}N_2$.HCl	8.31	8.30	10.52	10.70		
Isobutyl	$N(CH_3)_2$	68	112-116	0.4	1.5012	242-242.8	$C_{16}H_{24}N_2$.HCl	[k]		12.63	12.53		
						150.6-152.5	$C_{17}H_{27}IN_2$	7.25	7.14			32.85	33.15
Isobutyl	$N(C_2H_5)_2$	81	114-118	0.05	1.4962	132.9-134	$C_{18}H_{28}N_2$.HCl	9.07	9.09	11.48	11.42		
						155.5-156.9	$C_{19}H_{31}IN_2$	6.76	6.72			30.63	30.60
Isobutyl	NC_5H_{10}[h]	79	136-142	0.05	1.5140	193.4-195.4	$C_{19}H_{28}N_2$.HCl	8.73	8.65	[l]			
						171.4-173	$C_{20}H_{31}IN_2$	[m]				29.77	29.62
β-Methallyl	NC_5H_{10}	72	141-150	1	1.5258	212.8-214.4	$C_{19}H_{26}N_2$.HCl	8.79	8.64	[n]			
Isobutenyl	NC_5H_{10}	75	136-139	0.1	1.5272	203-204.5	$C_{19}H_{26}N_2$.HCl	8.79	8.60	11.12	11.12		
						199.7-201	$C_{20}H_{29}IN_2$	6.60	6.48			29.91	29.85

[a] NC_4H_8 = 1-pyrrolidyl. [b] Base m.p. 73-74°. Ref. 4 reported m.p. 71.5-72.5°. [c] *Anal.* Calcd.: C, 73.49; H, 7.09. Found: C, 73.76; H, 7.22. [d] Methiodides were recrystallized from ethyl acetate containing a small amount of methanol. [e] Where no boiling point is given the basic nitrile was used without distillation. [f] Hydrochloride would not crystallize. [g] $NC_4H_7CH_3$ = 2-methyl-1-pyrrolidyl. [h] NC_5H_{10} = 1-piperidyl. [i] *Anal.* Calcd.: C, 69.72; H, 8.61. Found: C, 69.55; H, 8.68. [j] Ref. 6 reported b.p. 180-185° (4 mm.). [k] *Anal.* Calcd.: C, 68.43; N, 8.97. Found: C, 68.56; H, 9.07. [l] *Anal.* Calcd.: C, 71.11; H, 9.11. Found: C, 71.16; H, 9.00. [m] *Anal.* Calcd.: C, 56.33; H, 7.33. Found: C, 56.55; H, 7.33. [n] *Anal.* Calcd.: C, 71.56; H, 8.54. Found: C, 71.65; H, 8.51.

It was found most convenient to prepare these 3-phenylpropylamines by alkylating the appropriate phenylacetonitrile with an aminoethyl chloride with the aid of sodium amide. The basic nitriles were then treated with excess sodium amide in order to replace the cyano group by hydrogen.[3] The aminoethyldiphenylacetonitriles were cleaved conven-

(1) Chilcott Laboratories, Division of The Maltine Company, Morris Plains, N. J.

(2) A. W. Ruddy and J. S. Buckley, Jr., THIS JOURNAL, **72**, 718 (1950).

(3) Report O. P. B. 981, Office of the Publication Board, Dept. of Commerce, pp. 41-42.

(4) D. J. Dupré, J. Elks, B. A. Hems, K. N. Speyer and R. M. Evans, *J. Chem. Soc.*, 500 (1949).

(5) M. Bockmühl and G. Ehrhart (to Winthrop Chemical Co., Inc.) U. S. Patent 2,230,774, Feb. 4, 1941.

(6) O. Eisleb, *Ber.*, **74B**, 1443 (1941).

After this work was begun an example of the 3-alkyl - 3 - phenylpropylamines was described by Bergel, *et al.*,[7] who prepared 3-phenylpentyldimethylamine from the corresponding nitrile by treatment with sodium and alcohol. In addition to the diphenyl- and cyclohexylphenylpropylamines previously described[2] there was recently reported[8] a number of diphenylpropylamines prepared by hydrogenation of the corresponding diphenylallylamines.

Since it is possible that the double bond might migrate in the conversion of 2-isobutenyl-2-phenyl-4-N-piperidylbutanenitrile into N - (5 - methyl - 3-phenyl-4-hexenyl)-piperidine the structure of the compound was proven in the following way. The ultraviolet absorption spectrum of the product was examined and no absorption indicative of a conjugated system was found.[9] Mild oxidation with potassium permanganate gave a volatile fragment which was identified as acetone by isolation as the insoluble dibenzal derivative. The corresponding 3-hexenylamine would be conjugated with the benzene ring and would produce isobutyraldehyde with a mild oxidizing agent.

All of the amine hydrochlorides and methiodides reported in Tables I and II were given a preliminary screening by Dr. A. M. Lands and his staff of our Pharmacology Department. The compounds were tested for their spasmolytic activity *in vitro* against spasms induced in isolated rabbit ileum by acetylcholine and

(7) F. Bergel, J. W. Haworth, A. L. Morrison and H. Rinderknecht, *J. Chem. Soc.*, 261 (1944).

(8) D. W. Adamson, *ibid.*, S 145 (1949).

(9) The author is grateful to Dr. F. C. Nachod and his staff for this information.

TABLE II

SUBSTITUTED 3-PHENYLPROPYLAMINES C_6H_5–CHR–CH_2–CH_2–Am

R	Am	Yield %	Base B.p., °C.	Mm.	$n^{25}D$	M.p., °C. (cor.)	Formula	Hydrochlorides and methiodides Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Chlorine, % Calcd.	Found	Iodine, % Calcd.	Found
Phenyl	$N(CH_3)_2$	91	116–120	1	[a]	169–170[b]	$C_{17}H_{21}N$·HCl	74.02	74.36	8.04	8.21	[c]			
						178.3–179.4[d]	$C_{18}H_{24}IN$	56.70	56.56	6.34	6.21			[e]	
Phenyl	NC_5H_{10}[f]	94	163–176	1	[g]	216–217[h]	$C_{20}H_{25}N$·HCl					11.23	11.12		
						175.3–176.3[i]	$C_{21}H_{28}IN$	59.86	59.95	6.70	6.62			30.12	30.43
Phenyl	NC_4H_8[j]	94	128–136	0.05	1.5637	159.2–160.4[k]	$C_{19}H_{27}N$·H_3PO_4					[l]			
						156.6–157[m]	$C_{20}H_{26}IN$	58.97	58.80	6.43	6.15			31.23	30.05
Phenyl	$NC_4H_7CH_3$[n]	81	162–167	1	1.5528	142–144	$C_{20}H_{25}N$·HCl	76.04	75.80	8.30	7.93	11.23	11.15		
						206.5–208	$C_{21}H_{28}IN$	59.85	59.77	6.69	6.70			30.12	30.24
Cyclohexyl	$N(CH_3)_2$	84	110–120	0.2	1.5150	154–155	$C_{17}H_{27}N$·HCl	72.44	72.30	10.01	9.94	12.58	12.44		
Cyclohexyl	$N(C_2H_5)_2$	82	144–155	1.5	1.5122	125.4–126.8	$C_{19}H_{31}N$·HCl	73.63	73.61	10.41	10.30	11.45	11.32		
Cyclohexyl	NC_4H_8[j]	81	125–127	0.1	1.5275	181.8–183.2	$C_{19}H_{29}N$·HCl	74.11	74.33	9.82	9.66	11.51	11.38		
Cyclohexyl	NC_5H_{10}[f]	95	128–132	0.05	1.5274	227–228[o]	$C_{20}H_{31}N$·HCl					11.01	10.97		
Cyclopentyl	$N(CH_3)_2$	82	103–108	0.3	1.5096	136.7–138.9	$C_{16}H_{25}N$·HCl	71.75	71.46	9.79	9.82	13.24	13.33		
						134.7–136.4	$C_{17}H_{28}IN$	54.69	54.60	7.56	7.46			34.00	33.80
n-Hexyl	$N(C_2H_5)_2$	72	123–126	1	1.4860	88.8–89.6	$C_{19}H_{33}N$·HCl	[p]				11.33	11.17		
n-Hexyl	NC_5H_{10}[f]	78	126–129	1	1.5009	179–180	$C_{20}H_{33}N$·HCl	74.15	73.90	10.58	10.50	10.94	10.92		
Isobutyl	$N(CH_3)_2$	90	74–75	0.3	1.4872	136–137.2	$C_{15}H_{25}N$·HCl	70.42	70.57	10.24	10.36	13.86	13.57		
						109.2–111	$C_{16}H_{28}IN$	53.18	53.30	7.81	7.69			35.13	34.86
Isobutyl	$N(C_2H_5)_2$	91	129–131	4	1.4852	105–106	$C_{17}H_{29}N$·HCl	71.93	72.12	10.65	10.58	12.49	12.30		
						115.6–116.8	$C_{18}H_{32}IN$	55.52	55.57	8.28	8.23			32.60	32.56
Isobutyl	NC_5H_{10}[f]	90	124–129	1	1.5035	205.8–207.2	$C_{18}H_{23}N$·HCl	73.06	73.32	10.22	9.97	11.98	11.98		
						103.1–104.6	$C_{19}H_{32}IN$	56.85	57.08	8.04	7.91			31.62	31.60
Methallyl	NC_5H_{10}	48	110–111	0.1	1.5199	199–200	$C_{18}H_{27}N$·HCl	73.56	73.61	9.60	9.35	12.07	11.76		
Isobutenyl	NC_5H_{10}	58	114–116	0.05	1.5196	198–199.7	$C_{18}H_{27}N$·HCl	73.56	73.41	9.60	9.60	12.07	11.90		
						127.5–129.5	$C_{19}H_{30}IN$	57.14	57.43	7.57	7.59			31.78	31.60

[a] M.p. 45–46°. [b] Ref. 8 reported m.p. 169–170°. [c] *Anal.* Calcd.: N, 5.08. Found: N, 5.03. [d] Ref. 8 reported m.p. 179–180°. [e] *Anal.* Calcd.: N, 3.67. Found: N, 3.54. [f] NC_5H_{10} = 1-piperidyl. [g] M.p. 40.5–41.5°. [h] Ref. 8 reported m.p. 215–217°; ref. 3, m.p. 215–216°; ref. 2, m.p. 216–217°. [i] Ref. 8 reported m.p. 175–176° dec. [j] NC_4H_8 = 1-pyrrolidyl. [k] I. G. Farbenindustrie A. G. French Patent 884,569 reported m.p. 160–161°. [l] *Anal.* Calcd.: H_3PO_4, 26.97. Found: H_3PO_4, 27.10. [m] Ref. 8 reported m.p. 156–157°. [n] $NC_4H_7CH_3$ = 2-methyl-1-pyrrolidyl. [o] Ref. 2 reported identical melting point. [p] *Anal.* Calcd.: N, 4.49. Found: N, 4.56.

barium chloride. The most active compound was N-(3-isobutyl-3-phenylpropyl)-piperidine hydrochloride which was 69 times as effective as papaverine against barium induced spasms and 9.5% as effective as atropine sulfate as an acetylcholine antagonist.

Acknowledgment.—The author is indebted to Mr. M. E. Auerbach and Mr. K. D. Fleischer and staff for the analytical data.

Experimental

Chloroethylamine Hydrochlorides.—Dimethylaminoethyl chloride and diethylaminoethyl chloride hydrochlorides are commercially available. 2-(N-Pyrrolidyl)-ethyl chloride,[10] and 2-(N-piperidyl)-ethyl chloride[11] hydrochlorides were prepared by published procedures. 2-(N-2-Methylpyrrolidyl)-ethyl chloride hydrochloride was prepared by treating 2-(N-2-methylpyrrolidyl)-ethanol[12] with thionyl chloride in chloroform and recrystallized from isopropyl alcohol-ethyl acetate.

Anal. Calcd. for $C_7H_{14}ClN.HCl$: N, 7.61; Cl, 38.52. Found: N, 7.84; Cl, 38.40.

The base distilled at 60–62° (8 mm.), $n^{25}D$ 1.4622.

Nitriles.—Diphenylacetonitrile is commercially available. Cyclohexylphenylacetonitrile,[13] cyclopentylphenylacetonitrile,[14] *n*-hexylphenylacetonitrile,[6] isobutylphenylacetonitrile[15] and isobutylidenephenylacetonitrile[16] were prepared by published procedures. β-Methallylphenylacetonitrile was prepared by treating β-methallyl chloride with phenylacetonitrile in benzene with the aid of sodium amide and distilling the product through a 30-cm. column packed with glass helices. β-Methallylphenylacetonitrile was obtained in 34% yield, b.p. 124–128° (5 mm.), $n^{25}D$ 1.5183.

Anal. Calcd. for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.29; H, 7.67; N, 8.07.

The reaction also produced a 29% yield of dimethallylphenylacetonitrile, b.p. 146–148° (5 mm.), $n^{25}D$ 1.5228.

Anal. Calcd. for $C_{16}H_{19}N$: C, 85.28; H, 8.49; N, 6.22. Found: C, 85.32; H, 8.48; N, 6.29.

Substituted α-(β-Aminoethyl)-phenylacetonitriles.—Diphenylacetonitrile was alkylated with the appropriate aminoethyl chloride by a published procedure.[3]

The alkyl- and cycloalkylphenylacetonitriles were prepared in the following manner. A mixture of 0.15 mole of aminoethyl chloride hydrochloride, 0.15 mole of alkylphenylacetonitrile and 0.3 mole of sodium amide in 200 ml. of dry benzene was stirred and gradually heated to about 60°. The exothermic reaction was then controlled by occasional cooling with an ice-bath. When the ammonia evolution had diminished the reaction was heated at 65° for about two hours. To the cooled mixture water was added and the benzene layer separated and washed with water. The product was then extracted with diluted hydrochloric acid, converted back to the base, extracted with ether and dried over sodium hydroxide pellets. After removing the solvent the product was distilled under reduced pressure. The yields of basic nitriles were generally good ranging from 68 to 90%. They are described in Table I.

3-Phenylpropylamines.—To a well stirred mixture of about 0.4 mole of sodium amide in 100 ml. of refluxing xylene was added, dropwise, a solution of 0.1 mole of a basic nitrile in 100 ml. of xylene. The reaction was vigorously stirred and refluxed for ten hours. The excess sodium amide was decomposed by the careful addition of water to the stirred mixture. The xylene layer was separated, washed with water and then extracted with diluted hydrochloric acid. The acid layer was made strongly basic with 35% sodium hydroxide, extracted with ether and the ether solution dried over sodium hydroxide pellets. The solvent was removed and the amine distilled under reduced pressure. The substituted 3-phenylpropylamines, obtained in yields of 48 to 95%, are described in Table II.

RENSSELAER, N. Y. RECEIVED FEBRUARY 28, 1951

(10) J. B. Wright, H. G. Kolloff and J. H. Hunter, THIS JOURNAL, **70**, 3098 (1948).

(11) F. F. Blicke and C. E. Maxwell, *ibid.*, **64**, 428 (1942).

(12) R. O. Clinton, U. J. Salvador and S. C. Laskowski, *ibid.*, **71**, 3366 (1949).

(13) W. E. Bachman, "Organic Syntheses," Vol. 25, John Wiley and Sons, Inc., New York, N. Y., 1945, p. 25.

(14) G. Vasiliu, V. Dumitrascu and H. Vulcan, Soc. Chim. România Sect. române Stiinte, *Bul. chim. pură apl.* (2) **3A**, 54 (1941–1942), *C. A.*, **38**, 5493 (1944).

(15) F. Bodroux and F. Taboury, *Bull. soc. chim. France*, [4] **7**, 668 (1910).

(16) J. V. Murray and J. B. Cloke, THIS JOURNAL, **58**, 2016 (1936).

[CONTRIBUTION FROM THE IPATIEFF HIGH PRESSURE AND CATALYTIC LABORATORY, DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY]

Study in Terpene Series. XI.[1] The Dehydroxymethylation of Bicyclic Primary Terpenic Alcohols by Hydrogenolysis in the Presence of Nickel Catalysts[2]

BY V. N. IPATIEFF, G. J. CZAJKOWSKI AND HERMAN PINES

The dehydroxymethylation of primary bicyclic alcohols to hydrocarbons containing one carbon atom less than the original alcohols has been studied. The catalysts used were nickel–Kieselguhr, Raney nickel and nickel–alumina. The alcohols investigated were: hydronopol, nopol, myrtanol and 2-methyl-5-hydroxymethylbicyclo[3.2.1]octane. The hydrogenolysis proceeded in most cases in good yields at 160–180° and 65–100 atmospheres of pressure. 2,2-Dimethylnorpinane formed from the hydrogenolysis of myrtanol, yielded isopropylbenzene on the dehydrogenation over platinum–alumina catalyst.

In previous papers[1,3] it was shown that, in the presence of nickel catalysts, primary alcohols yield hydrocarbons having one less carbon atom. The extensive isomerization that occurs during many reactions in the terpene series made it of interest to ascertain if the cleavage of primary bicyclic terpene alcohols is accompanied by isomerization. Nickel-kieselguhr,[4] nickel–alumina[1] (77% NiO–23% Al_2O_3) and W-6 Raney nickel,[5] containing alumina,[6] were used as catalysts. The following alcohols were investigated: hydronopol,[7] nopol,[7] myrtanol and 2-methyl-5-hydroxymethyl-bicyclo[3.2.1]octane.[8] The latter compound was prepared by hydrogenating the unsaturated aldehyde obtained from the selenium dioxide oxidation of 2,6-dimethyl-2-bicyclo[3.2.1]octene.[9]

(1) For paper X of this series, see V. N. Ipatieff, W. W. Thompson and H. Pines, THIS JOURNAL, **73**, 553 (1951).

(2) This work was made possible through the financial assistance of Universal Oil Products Company, Chicago, Illinois.

(3) V. N. Ipatieff, G. S. Monroe, L. E. Fischer and E. E. Meisinger, *Ind. Eng. Chem.*, **41**, 1802 (1949).

(4) V. N. Ipatieff and B. B. Corson, *ibid.*, **30**, 1039 (1931).

(5) H. Adkins and H. R. Billica, THIS JOURNAL, **70**, 695 (1948).

(6) V. N. Ipatieff and H. Pines, *ibid.*, **72**, 5320 (1950).

(7) J. P. Bain, *ibid.*, **68**, 638 (1946).

(8) V. N. Ipatieff, J. E. Germain, W. W. Thompson and H. Pines, unpublished results.

(9) V. N. Ipatieff, H. Pines, V. Dvorkovitz, R. C. Olberg and M. Savoy, *J. Org. Chem.*, **12**, 34 (1947).