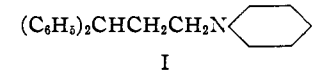
[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Antispasmodics. N-(3-Phenylpropyl)-amines and 3-Amino-1-phenyl-1-propanols[1]

BY A. WAYNE RUDDY AND JAY S. BUCKLEY, JR.[2]

The spasmolytic activity of N-(3,3-diphenylpropyl)-piperidine, I, which is one of the active constituents of the product "Aspasan,"[3] aroused our interest in compounds of this type. In an attempt to determine the effect on spasmolytic activity of alteration in structure of I, the preparation of a number of 3-phenylpropylamines and 3-amino-1-phenyl-1-propanols was undertaken. The structure of I was altered by (1) replacing one



I

phenyl group by hydrogen, isopropyl, isobutyl, *n*-hexyl, cyclohexyl or thienyl radicals, (2) substituting the hydrogen of the propyl chain by methyl, ethyl and hydroxyl groups, (3) replacing piperidine by dimethylamine, diethylamine and morpholine. After a great deal of our work had been completed, the pharmacological activity of a number of such compounds was published.[4] Since then patents have been issued describing the chemistry of several N-(3,3-diphenylpropyl)-amines[5] and two 3-amino-1,1-diphenyl-1-propanols.[6]

N-(3-Phenylpropyl)-piperidine has been prepared by a reaction of β-phenylethylmagnesium bromide with isobutoxymethylpiperidine[7] and by a catalytic hydrogenation of 1,3-dipiperidino-1-phenyl-2-propene.[8] In these laboratories it was found more convenient to prepare N-(3-phenylpropyl)-piperidine by chlorinating 1-phenyl-3-(1-piperidyl)-1-propanol with thionyl chloride; the product, N-(3-chloro-3-phenylpropyl)-piperidine, was dehalogenated in 94% yield by hydrogenating in the presence of a buffered palladium-on-charcoal catalyst. N-(2-Methyl-3-phenylpropyl)-piperidine was prepared in the same manner.

Eisleb[9] has described the condensation of diphenylmethane and fluorene with diethylaminoethyl chloride in the presence of sodamide. In the present work the method of Bockmühl, *et al.*,[5] was used for the preparation of diphenylmethyl sodium which was condensed with N-(3-chloro-2-butyl)-piperidine in 17% yield. This method was abandoned because of the poor yield obtained.

Several of the amines were obtained from 3-amino-1-phenyl-1-propanols, two of which had been prepared previously by adding phenylmagnesium bromide to dialkylaminopropionates.[6] In our method of preparation there was required, as intermediates, a number of aryl α-alkyl-β-aminoalkyl ketones. These were obtained conveniently when the Mannich reaction was carried out on 2-propiothienone, propiophenone, butyrophenone and isobutyrophenone. As can be seen in Table I, the yields of product from the last three ketones were found to decrease in this order.

Because they usually decomposed during distillation, the Mannich bases from methyl aryl ketones, with few exceptions, have been purified by recrystallization as their hydrochlorides. In contrast, it was found that the products from propiophenone, butyrophenone and 2-propiothienone were quite stable to distillation at 1 mm. of pressure. However, they did decompose slowly upon long standing. All of the Mannich bases were purified by distillation, and most of them then formed crystalline hydrochlorides.

The aminoalcohols were prepared by adding the Mannich bases or their hydrochlorides to various Grignard reagents. It has since been revealed that this general method has been described by Bockmühl and Stein,[10] but no details are available. When the aminoketone contains an alkyl group on the alpha carbon atom the aminoalcohols are obtained in excellent yields. However, when the alpha carbon is unsubstituted the yields are variable depending on which Grignard reagent is used.

A number of these aminoalcohols were treated with red phosphorus and hydriodic acid to produce the corresponding N-(3-phenylpropyl)-amines. This procedure gave yields of 73–94% of distilled base. Although only one of the possible racemates was formed in production of the 3-amino-2-alkyl-1-cyclohexyl-1-phenyl-1-propanols, the phosphorus and hydriodic acid treatment of them produced a partial inversion at the carbon atom originally bearing the hydroxyl group. Fractional crystallization of the N-(2-alkyl-3-cyclohexyl-3-phenylpropyl)-piperidine hydrochlorides gave the low- and high-melting salts corresponding to the two possible racemates. Attempted bromination and catalytic hydrogenation demonstrated that these compounds were saturated.

Every phosphorus and hydriodic acid reaction that was carried out gave the expected products with one exception. In the treatment of 1-cyclohexyl-1-phenyl-3-(1-piperidyl)-1-propanol there were obtained two unsaturated hydrochlorides;

(1) Presented in part before the Division of Medicinal Chemistry, American Chemical Society, Chicago, Illinois, September 12, 1946.

(2) Present address: Department of Chemistry, University of Minnesota, Minneapolis, Minnesota.

(3) *Chem. Zentr.*, **113**, I, 3019 (1942); **113**, 2054 (1942).

(4) Report No. PB 981, Office of the Publication Board, Dept. of Commerce, pp. 38–43.

(5) Bockmühl, Ehrhart, Eisleb and Stein, U. S. Patent 2,446,522 (Aug. 10, 1948).

(6) I. G. Farben, Swiss Patents 234,785 (Feb. 16, 1945) and 240,363 (May 16, 1946).

(7) Pollard and Robinson, *J. Chem. Soc.*, 2770 (1927).

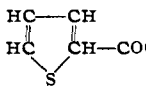
(8) Mannich, Handke and Roth, *Ber.*, **69**, 2112 (1936).

(9) Eisleb, *ibid.*, **74**, 1433 (1941).

(10) Bockmühl and Stein, German Patent application 70,236, Aug. 11, 1941; Report No. PB 981, Office of the Publication Board, Dept. of Commerce, p. 118.

TABLE I

ARYL α-ALKYL-β-AMINOALKYL KETONES

$C_6H_5COCRR'CH_2R''$ R	R'	R''	Base Yield, %	Base B. p., °C. (1 mm.)	Base $n^{25}D$	Hydrochloride M. p., °C. (cor.)	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
CH_3	H	$N(CH_3)_2$	74	80–82	1.5162	153–154[a]	$C_{12}H_{17}NO\cdot HCl$	6.15	6.02	15.57	15.52
CH_3	H	$N(C_2H_5)_2$	52	103–105	1.5061	131–132.5	$C_{14}H_{21}NO\cdot HCl$	5.48	5.60	13.86	13.84
CH_3	H	$N(n\text{-}C_4H_9)_2$	49	140–144	1.4950	[b]					
CH_3	H	NC_5H_{10}[c]	69	120	1.5272	176.2–177	$C_{15}H_{21}NO\cdot HCl$	[d]		13.24	13.27
CH_3	H	NC_4H_8O[c]	73	135–138	1.5316	172–173.5	$C_{14}H_{19}NO_2\cdot HCl$	5.19	5.07	13.14	13.40
C_2H_5	H	$N(CH_3)_2$	39	110[e]		144–145[f]	$C_{13}H_{19}NO\cdot HCl$	5.79	5.70	14.67	14.65
C_2H_5	H	$N(C_2H_5)_2$	29	107	1.5038	127–128.5	$C_{15}H_{23}NO\cdot HCl$	5.19	5.08	13.14	13.31
C_2H_5	H	$N(n\text{-}C_4H_9)_2$	35	128–132	1.4943	[g]					
C_2H_5	H	NC_5H_{10}	60	124–126[h]	1.5242	143.4–145	$C_{16}H_{23}NO\cdot HCl$	[i]		12.58	12.55
C_2H_5	H	NC_4H_8O	62	131–134	1.5264	165–167	$C_{15}H_{21}NO_2\cdot HCl$	4.94	4.64	12.49	12.68
CH_3	CH_3	NC_5H_{10}	11	116–120	1.5216	158–159	$C_{16}H_{23}NO\cdot HCl$	[j]		12.58	12.66
								Sulfur, % Calcd.	Sulfur, % Found	Chlorine, % Calcd.	Chlorine, % Found
CH_3	H	$N(CH_3)_2$	77	92–98	1.5365	158–158.5[k]	$C_{10}H_{15}NOS\cdot HCl$	13.72	13.74	15.17	15.09
CH_3	H	$N(C_2H_5)_2$	77	108–111	1.5233	117–119	$C_{12}H_{19}NOS\cdot HCl$	12.24	12.22	13.54	13.60
CH_3	H	NC_5H_{10}	66	118–123	1.5450	171–172	$C_{13}H_{19}NOS\cdot HCl$	11.71	11.56	12.95	12.92

[a] Burckhalter and Fuson, THIS JOURNAL, **70**, 4184 (1948), reported m. p. 150–154° and a yield of 83%. [b] Hydrochloride would not crystallize; picrate, m. p. 105–106.5°. *Anal.* Calcd. for $C_{24}H_{32}N_4O_8$: C, 57.13; H, 6.39. Found: C, 57.12; H, 6.02. [c] NC_5H_{10} = piperidino, NC_4H_8O = morpholino. [d] *Anal.* Calcd.: C, 67.27; H, 8.28. Found: C, 67.16; H, 8.15. [e] M. p. 43–45°. [f] Burckhalter and Fuson, ref. *a*, reported m. p. 140–141° and a yield of 60%. [g] Hydrochloride would not crystallize; picrate, m. p. 116.5–117.5°. *Anal.* Calcd. for $C_{25}H_{34}N_4O_8$: C, 57.90; H, 6.61. Found: C, 58.10; H, 6.35. [h] M. p. 31–32°. [i] *Anal.* Calcd.: C, 68.19; H, 8.58. Found: C, 68.34; H, 8.50. [j] *Anal.* Calcd.: C, 68.19; H, 8.58. Found: C, 68.06; H, 8.41. [k] Blicke and Burckhalter, THIS JOURNAL, **64**, 451 (1942), reported m. p. 154–156° and a yield of 60%.

A, m. p. 236–238°, and B, m. p. 190–191°. Both compounds added one mole of hydrogen in the presence of palladium-on-charcoal, indicating one double bond, and produced the same hydrochloride m. p. 227–228°. This is identical with N-(3-cyclohexyl-3-phenylpropyl)-piperidine hydrochloride obtained by saturating one ring of N-(3,3-diphenylpropyl)-piperidine. Compound A has been identified as N-[3-(Δ¹-cyclohexenyl)-3-phenylpropyl]-piperidine by Jackman, Nachod and Archer.[11] The structure of Compound B is still unknown.

The spasmolytic activity *in vitro* of the piperidine compounds has been presented by Becker, *et al.*,[12] of these laboratories. In general, it can be stated that branching of the propyl chain appears to decrease spasmolytic activity, substitution of cyclohexyl for one phenyl group increases both musculotropic and neurotropic activity and introduction of a hydroxyl group increases the neurotropic activity.

Experimental

N-(3-Phenylpropyl)-piperidine.—To 1-phenyl-3-(1-piperidyl)-1-propanol[13] in chloroform was added an excess of thionyl chloride and the reaction refluxed until completed. It was then taken to dryness under reduced pressure and the residue crystallized by dissolving in hot alcohol and diluting with ethyl acetate.

An aqueous solution of the N-(3-chloro-3-phenylpropyl)-piperidine hydrochloride was hydrogenated at three atmospheres in the presence of buffered palladium-on-charcoal catalyst.[14] The product was purified by distilling the base and reconverting to the hydrochloride.

N-(2-Methyl-3-phenylpropyl)-piperidine was prepared in a similar manner. See compounds No. 1, 2, 3 and 4 of Table II.

3-(1-Piperidyl)-2-butanol.—To a 50% aqueous solution of piperidine was added 2,3-epoxybutane[15] and after warming for an hour the aminoalcohol was salted out with sodium hydroxide. It was dried over potassium hydroxide and then distilled, b. p. 87–90° (10 mm.), $n^{20}D$, 1.4640. The yield of 3-(1-piperidyl)-2-butanol was 79%. It was converted to its hydrochloride m. p. 148–149.5°.

Anal. Calcd. for $C_9H_{19}NO\cdot HCl$: Cl, 18.30; N, 8.91. Found: Cl, 18.27; N, 8.85.

N-(3-Chloro-2-butyl)-piperidine.—The aminoalcohol hydrochloride was treated with thionyl chloride, in the manner described above, and gave N-(3-chloro-2-butyl)-piperidine, b. p. 76–79° (8 mm.), $n^{20}D$ 1.4705, in 58% yield. Its hydrochloride melted 169–171°.

Anal. Calcd. for $C_9H_{18}ClN\cdot HCl$: Cl, 33.42; N, 6.60. Found: Cl, 33.47; N, 6.51.

N-(3,3-Diphenyl-1-methyl-2-methylpropyl)-piperidine.—The procedure followed for the condensation was essentially that of Bockmühl, *et al.*[5] To 0.9 mole of sodium sand under dry toluene was added 0.4 mole of chlorobenzene. After about thirty minutes a vigorous reaction took place which required external cooling. The mixture was heated at 50° for two hours and then 0.4 mole of diphenylmethane added. After heating for two more hours at 70° the mixture was cooled to 40° and 0.33 mole of N-(3-chloro-2-butyl)-piperidine was added. When the reaction temperature started to fall the mixture was heated at 80° for one hour. The excess sodium was decomposed under nitrogen by the careful addition of water. The toluene layer was washed with water and then extracted

(11) Jackman, Nachod and Archer, THIS JOURNAL, **72**, 716 (1950).

(12) Becker, Ananenko, Glenwood and Miller, *Federation Proc.*, **5**, 163 (1946).

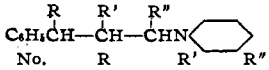
(13) Mannich and Lammering, *Ber.*, **55**, 3510 (1922).

(14) Levin, Graham and Kolloff, *J. Org. Chem.*, **9**, 381 (1944).

(15) Winstein and Lucas, THIS JOURNAL, **61**, 1576 (1939).

TABLE II

N-(3-PHENYLPROPYL)-PIPERIDINES



No.	R	R′	R″	Base B. p., °C. (1 mm.)	Base $n^{25}D$	Yield, %	Hydrochloride M. p., °C. (cor.)	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
1	Cl	H	H			94	158–158.5	$C_{14}H_{20}ClN\cdot HCl$			25.86	25.75
2	Cl	CH_3	H			74	162–163	$C_{15}H_{22}ClN\cdot HCl$			24.60	24.67
3	H	H	H	100–102[a]	1.5172	94	185–186	$C_{14}H_{21}N\cdot HCl$	[b]		14.72	14.78
4	H	CH_3	H	106–107	1.5105	93	181–182	$C_{15}H_{23}N\cdot HCl$	5.52	5.49	13.79	14.00
5	C_6H_5	H	H	183–184[c]		97	216–217[d]	$C_{20}H_{25}N\cdot HCl$			11.23	11.12
6	C_6H_9[e]	H	H	148–154[f]	1.5402	73	236–238	$C_{20}H_{29}N\cdot HCl$	4.38	4.30	11.08	11.07
7	C_6H_{11}[e]	H	H	164–167	1.5265	86	227–228	$C_{20}H_{31}N\cdot HCl$[g]	4.35	4.31	11.01	10.97
8	C_6H_5	CH_3	H	[h]		80	218–220[i]	$C_{21}H_{27}N\cdot HCl$	4.25	4.45	10.75	10.78
9	I C_6H_{11}	CH_3	H	160–161[j]	1.5365	18	178–180	$C_{21}H_{33}N\cdot HCl$	4.17	4.17	10.55	10.68
10	II C_6H_{11}	CH_3	H			32	223–225	$C_{21}H_{33}N\cdot HCl$	4.17	4.02	10.55	10.60
11	C_6H_5	CH_3	CH_3	154–160	1.5595[k]	17	198.5–200	$C_{22}H_{29}N\cdot HCl$[l]	4.07	4.03	10.31	10.28
12	C_6H_5	C_2H_5	H	[m]		83	195–196	$C_{22}H_{29}N\cdot HCl$	4.07	4.09	10.31	10.29
13	I C_6H_{11}	C_2H_5	H	[n]		24	148.5–150	$C_{22}H_{35}N\cdot HCl$	4.00	3.85	10.13	10.16
14	II C_6H_{11}	C_2H_5	H			17	211.5–213	$C_{22}H_{35}N\cdot HCl$	4.00	4.04	10.13	10.01

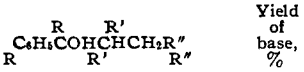
[a] Ref. 7 reported b. p. 150° (15 mm.), picrate m. p. 99–100°. [b] *Anal.* Calcd.: C, 70.15; H, 9.18. Found: C, 70.23; H, 9.21. [c] B. p. at 1.5 mm.; base m. p. 41–42.5°. Prepared from β-(N-piperidyl)-ethyldiphenylacetonitrile by the procedure of ref. 4. Ref. 5 reported b. p. 210–220° (8 mm.). [d] Ref. 4 reported m. p. 215–216°. Ref. 5 reported m. p. 214–215°. [e] C_6H_9 = Δ¹-cyclohexenyl, C_6H_{11} = cyclohexyl. [f] B. p. at 0.3 mm. [g] *Anal.* Calcd.: C, 74.61; H, 10.02. Found: C, 74.68; H, 9.94. [h] Base m. p. 99–100°. [i] Ref. 5 reported b. p. 220–230° (13 mm.), hydrochloride m. p. 211–212°. [j] Base mixture obtained in 85% yield. [k] Index at 20°. [l] *Anal.* Calcd.: C, 76.82; H, 8.79. Found: C, 76.77; H, 8.72. [m] Base m. p. 68–69°. [n] Hydriodide of mixed racemates was obtained in 93% yield.

with dilute hydrochloric acid. The acid extracts were made alkaline and the base extracted with ether. After drying over potassium carbonate the ether was removed and the residue distilled under reduced pressure (see compound No. 11 of Table II).

Aryl α-Alkyl-β-aminoalkyl Ketones.—The amounts of reactants and time of heating were the same as those described by Mannich and Lammering.[13] When the condensation was finished, the alcohol and diethylformal were completely removed under reduced pressure. The residue was dissolved in water and extracted with ether. The aqueous solution was made alkaline with sodium hydroxide, and the liberated base was extracted with ether. After drying over potassium carbonate the ether was removed and the base distilled under reduced pressure. The products from this reaction are described in Table I.

TABLE III

3-AMINO-1-PHENYL-1-PROPANOLS



No.	R	R′	R″	Yield of base, %	Base, m. p. °C. (cor.)	Hydrochlorides M. p., °C. (cor.)	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
1	*i*-C_3H_7	H	NC_5H_{10}[a]	12	75–76	189–190	$C_{17}H_{27}NO\cdot HCl$[b]	4.70	4.65	11.90	11.88
2	*i*-C_4H_9	H	NC_5H_{10}[c]	50	59–60	229–231	$C_{18}H_{29}NO\cdot HCl$	[d]		11.37	11.22
3	*n*-C_6H_{13}	H	NC_5H_{10}	74	66–68	214–215	$C_{20}H_{33}NO\cdot HCl$	4.12	4.23	10.43	10.25
4	C_6H_{11}[a]	H	NC_5H_{10}[e]	10	114–115	245–246	$C_{20}H_{31}NO\cdot HCl$	4.15	4.12	10.49	10.42
5	C_6H_5	H	NC_5H_{10}	35	115.5–116.5[f]	229–230	$C_{20}H_{25}NO\cdot HCl$	4.22	4.02	10.68	10.71
6	C_6H_{11}	CH_3	NC_5H_{10}	94	117–118	258–259	$C_{21}H_{33}NO\cdot HCl$	3.98	4.08	10.07	10.11
7	C_6H_5	CH_3	NC_5H_{10}	88	120–121	215–216	$C_{21}H_{27}NO\cdot HCl$	4.05	3.98	10.25	10.29
8	C_6H_{11}	C_2H_5	NC_5H_{10}	89	86–87[g]	237–238.5	$C_{22}H_{35}NO\cdot HCl$	3.85	4.01	9.69	9.72
9	C_6H_5	C_2H_5	NC_5H_{10}	86	122–124	211–212	$C_{22}H_{29}NO\cdot HCl$	[h]		9.85	9.96
10	C_4H_3S[a]	CH_3	NC_5H_{10}	86	103.5–104	175–176	$C_{19}H_{25}NOS\cdot HCl$	[i]		10.07	10.27
11	C_6H_{11}	H	$N(CH_3)_2$	12	[j]	212–213	$C_{17}H_{27}NO\cdot HCl$	4.70	4.69	11.90	11.84
12	C_6H_5	CH_3	$N(CH_3)_2$	71	93–94	237.5–238	$C_{18}H_{23}NO\cdot HCl$	4.55	4.49	11.59	11.41
13	C_6H_{11}	CH_3	$N(CH_3)_2$	76	105–106	253–254	$C_{18}H_{29}NO\cdot HCl$	4.49	4.38	11,37	11.24
14	C_6H_5	C_2H_5	$N(CH_3)_2$	78	103–104	197.5–198	$C_{19}H_{25}NO\cdot HCl$	4.38	4.33	11.08	11.02
15	C_6H_{11}	C_2H_5	$N(CH_3)_2$	92	70.5–71[k]	248.5–249.5	$C_{19}H_{31}NO\cdot HCl$	4.27	4.15	10.88	10.64
16	C_6H_5	CH_3	$N(C_2H_5)_2$	83	77–78	183–184.5	$C_{20}H_{27}NO\cdot HCl$	4.20	4.09	10.62	10.76
17	C_6H_{11}	CH_3	$N(C_2H_5)_2$	90	57–57.5[l]	141–142	$C_{20}H_{33}NO\cdot HCl$	4.12	4.06	10.43	10.32
18	C_6H_{11}	C_2H_5	$N(C_2H_5)_2$	93	56–57[m]	205–206.5	$C_{21}H_{35}NO\cdot HCl$	3.96	3.79	10.02	9.86
19	C_6H_5	CH_3	NC_4H_8O[a]	89	120–121	204–205	$C_{20}H_{25}NO_2\cdot HCl$	4.03	4.15	10.19	10.31

[a] NC_5H_{10} = piperidino, C_4H_3S = 2-thienyl, NC_4H_8O = morpholino, C_6H_{11} = cyclohexyl. [b] *Anal.* Calcd.: C, 68.54; H, 9.47. Found: C, 68.37; H, 9.28. [c] Methiodide, m. p. 194–195.5°. *Anal.* Calcd. for $C_{19}H_{32}INO$: C, 54.67; H, 7.73; I, 30.41. Found: C, 54.69; H, 7.50; I, 30.73. [d] *Anal.* Calcd.: C, 69.37; H, 9.70. Found: C, 69.40; H, 9.52. [e] Methiodide, m. p. 204.5–206.5°. *Anal.* Calcd. for $C_{21}H_{34}INO$: C, 56.88; H, 7.73; N, 3.16. Found: C, 57.02; H, 7.61; N, 3.12. [f] Ref. 6 gives base m. p. 119–120°, hydrochloride m. p. 216°. [g] B. p. 175–185° (1 mm.). [h] *Anal.* Calcd.: C, 73.41; H, 8.40. Found: C, 73.64; H, 8.56. [i] *Anal.* Calcd.: S, 9.11. Found: S, 9.13. [j] Isolated and purified as the hydrochloride. [k] B. p. 142–144° (1 mm.). [l] B. p. 149–152° (1 mm.). [m] B. p. 160–162° (1 mm.).

Aminophenylpropanols.—To a solution of 0.6 mole of Grignard reagent in ether was added 150 ml. of dry benzene. Then keeping the inner temperature at 0° or below there was added 0.25 mole of Mannich base or 0.2 mole of the corresponding hydrochloride. Heat was then applied and the ether removed until the inner temperature reached 65°. The mixture was hydrolyzed by pouring into a cold solution of ammonium chloride. The benzene layer was separated, washed with water and dried over potassium carbonate. After removing the solvent, the lower-boiling materials were removed under reduced pressure and the residue was recrystallized from methanol. Those amino-alcohols which were slow to crystallize were purified by distilling under reduced pressure. The products are described in Table III.

Substituted 3-Phenylpropylpiperidines.—A mixture of 0.7 mole of a substituted 1-phenyl-3-(1-piperidyl)-1-propanol, 0.9 mole of red phosphorus and 1.15 moles of 47% hydriodic acid in 550 ml. of glacial acetic acid was refluxed for three hours. The hot solution was filtered through a sintered glass funnel and the filtrate diluted with 1500 ml. of water and cooled. The hydriodide was filtered and washed with cold water, then resuspended in water and made strongly alkaline with sodium hydroxide. The liberated base was extracted with ether and dried over potassium carbonate. The ether was removed and the product distilled under reduced pressure. The products were converted to their hydrochlorides, and when racemates were present they were separated as their hydrochlorides by fractional crystallization. The products are described in Table II.

N-(3-Cyclohexyl-3-phenylpropyl)-piperidine.—N-(3,3-Diphenylpropyl)-piperidine[4] was hydrogenated by the method of Zenitz, *et al.*,[16] until three moles of hydrogen had been added and the hydrogenation had ceased. The product was purified by distilling under reduced pressure and then converting to its hydrochloride. See compound no. 7 of Table II.

Acknowledgments.—The authors are indebted to Dr. C. M. Suter for his guidance of the problem, to Mrs. M. Wilson for technical assistance and to Mr. M. E. Auerbach and his staff for the analytical data.

Summary

1. A number of N-(3-phenylpropyl)-amines have been described.

2. The Mannich reaction has been utilized to prepare new aryl α-alkyl-β-aminoalkyl ketones.

3. These aminoketones have been used in the preparation of a number of 3-amino-1-phenyl-1-propanols.

(16) Zenitz, Macks and Moore, THIS JOURNAL, **69**, 1117 (1947).

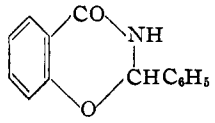
RENSSELAER, NEW YORK RECEIVED MAY 10, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, THE ABBOTT RESEARCH LABORATORIES]

The Condensation of Salicylamide with Aldehydes and Ketones

BY BRUCE W. HORROM AND HAROLD E. ZAUGG

The reaction of salicylamide with benzaldehyde to give 2-phenyl-2,3-dihydro-1,3,4-benzoxaz-4-one



I

was discovered independently by Titherley[1] and by Keane and Nicholls.[2] The latter workers also reported the same reaction with anisaldehyde. Since then the only extension of this reaction to other aldehydes has been with *m*-nitrobenzaldehyde,[3] chloral,[4] acetaldehyde,[5] isobutyraldehyde[6] and isovaleraldehyde.[6] In addition, the reactions of 5-chloro- and 5-bromosalicylamides with benzaldehyde have been described,[7] as well as the condensations of 3,5-dichlorosalicylamide[8] and 5-acetamidosalicylamide[9] with chloral. All of the reactions with chloral, in contrast with other carbonyl compounds, required dehydration by concentrated sulfuric acid of the first-formed acyclic chloral–salicylamide derivatives in order to bring about ring closure to the dihydrobenzoxazones. The only published case of the participation of a ketone in this reaction seems to be that of acetone.[10] A closely related reaction has been noted recently[11] in which treatment of salicylamide with vinyl acetate gave the same 2-methyldihydrobenzoxazone as the one obtained by Hicks[5] in the reaction with acetaldehyde.

The present work was undertaken when the observation was made[12] that the 2-phenyldihydrobenzoxazone I, in spite of its insolubility, showed analgesic activity in dogs of the same order as that of salicylamide.[13] In addition to the resynthesis of all of the above unsubstituted salicylamide derivatives, a number of new reaction products of salicylamide with aldehydes (Table I), ketones (Table II), and cyclic ketones (Table III) is reported. Although several derivatives were equal to it, none of them showed anal-

(1) Titherley, *J. Chem. Soc.*, **91**, 1425 (1907).

(2) Keane and Nicholls, *ibid.*, **91**, 266 (1907).

(3) Glaser and Frisch, *Arch. Pharm.*, **266**, 103 (1928).

(4) Kaufmann, *ibid.*, **265**, 226 (1927).

(5) Hicks, *J. Chem. Soc.*, **97**, 1032 (1910).

(6) Moucka and Rögl, *Ber.*, **59**, 756 (1926).

(7) Titherley and Hughes, *J. Chem. Soc.*, **97**, 1368 (1910); **99**, 23 (1911).

(8) Hirwe and Rana, *J. Univ. Bombay*, **8**, 243 (1939); *C. A.*, **34**, 2819 (1940).

(9) Rana, *J. Indian Chem. Soc.*, **19**, 299 (1942); *C. A.*, **37**, 2361 (1943).

(10) Fischer, Dangschat and Stettiner, *Ber.*, **65**, 1032 (1932).

(11) Mowry, Yanko and Ringwald, THIS JOURNAL, **69**, 2358 (1947).

(12) The authors are indebted to Dr. R. K. Richards and Mr. K. E. Kueter of the Abbott Pharmacological Research Department for the analgesic tests.

(13) Kaufmann[4] had prepared the chloral derivatives of salicylamide for testing as an analgesic, apparently with negative results. Early in the present work the preparation of this compound was repeated. It proved to be completely inactive.