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The Synthesis of Phencyclidine and Other 1-Arylcyclohexylamines

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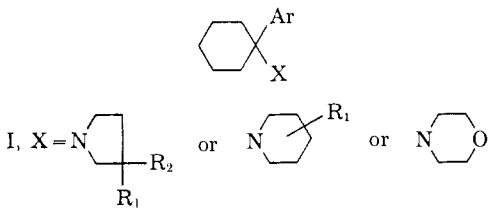
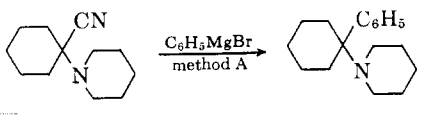
Various 1-arylcyclohexylamines were synthesized for evaluation as central nervous system depressants. The compounds were prepared by several procedures. 1-(1-Phenylcyclohexyl)piperidine, the first compound of this type synthesized, was prepared from 1-piperidinocyclohexanecarbonitrile by replacement of the cyano group by phenyl using phenylmagnesium bromide. These compounds were tested for cataleptoid activity and antitonic extensor properties.

During an investigation of the reaction of Grignard reagents with hindered nitriles, 1-piperidinocyclohexanecarbonitrile[1] was employed. The product formed by the reaction with phenylmagnesium bromide, 1-(1-phenylcyclohexyl)piperidine hydrochloride, was found to be a potent anesthetic agent in animals without significant effect on the respiration, heart rate, blood pressure, and body temperature.[2] Clinical application of phencyclidine[3] at total doses ranging from 0.138–1 mg./kg. of body weight produced profound analgesia without depression of circulation, respiration, or disturbance of cardiac rhythm.[4] Additional applications in human therapy are recorded.[5]

Various other 1-arylcyclohexylamines have been prepared in these laboratories in the past several years. Several synthetic routes were investigated. One method, applicable to the preparations of compounds of type I possessing cyclic amines, consisted of the replacement of the cyano group of the corresponding 1-cyclic-

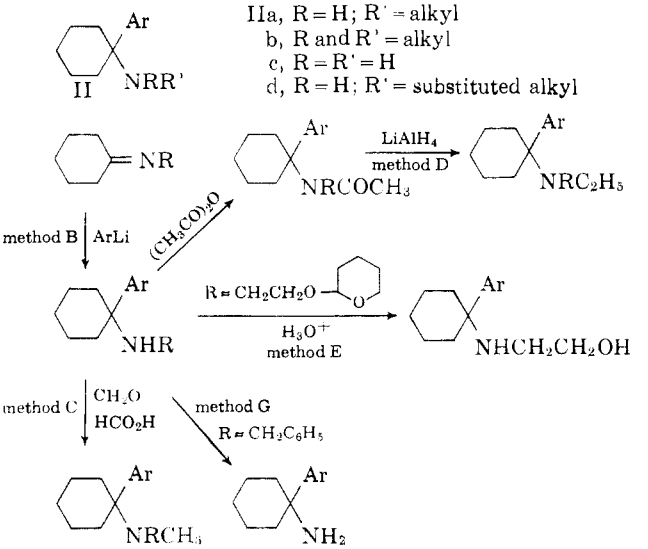


aminocyclohexanecarbonitrile by arylmagnesium halide (method A), as illustrated below for phencyclidine.



Alternatively, this compound was prepared by allowing phenylmagnesium halide to react with a salt of 1-(1-cyclohexenyl)piperidine. This reaction appears to proceed *via* an attack by the nucleophilic Grignard reagent on the tertiary imminium compound.

The procedures employed for the preparation of arylcyclohexylamines of type IIa–d are illustrated by methods B–E and G.



The arylcyclohexylamines of type IId were prepared by method B. For secondary amines of type IId with a hydroxyl group in the side chain, a tetrahydropyranyl ether was used as a protecting group (method E). Thus, 2-cyanomethoxytetrahydropyran[6] was reduced to the amine with lithium aluminum hydride, which in turn was treated with cyclohexanone to afford cyclohexylidene-β-tetrahydropyranyl-2-oxyethylamine. Further reaction with phenyllithium followed by acid hydrolysis gave N-(β-hydroxyethyl)-1-phenylcyclohexylamine.

A survey of the literature indicated that one of the members of the type IIc series, namely 1-phenylcyclohexylamine, had been reported in 1907 by Kursanov.[7] His method was based on the sealed-tube nitration of

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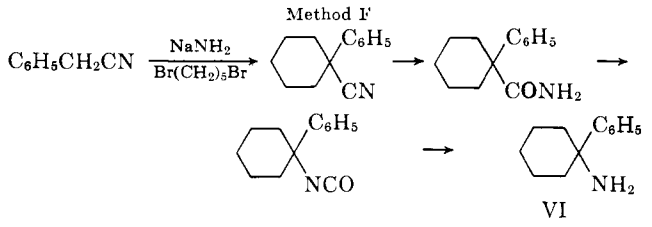
(2) G. Chen, *Federation Proc.*, **17**, 358 (1958).
(3) Sernyl or Sernylan® is the Trademark for phencyclidine, 1-(phenylcyclohexyl)piperidine hydrochloride.
(4) F. E. Greifenstein, M. DeVault, J. Yoshitake, and J. E. Gajewski, *Anesthesia Analgesia, Current Res.*, **37**, 283 (1958).
(5) (a) M. Johnstone, V. Evans, and S. Baigel, *Brit. J. Anaesthesia*, **31**, 433 (1959); (b) I. M. Riffin, *J. Med. Soc. N. J.*, **57**, 15 (1960); (c) A. J. Catenacci, D. D. Grove, W. A. Weiss, S. M. Fisher, A. M. Sismondo, and J. H. Meyer, *Antibiot. Med. Clin. Therapy*, **6**, 145 (1959); (d) M. W. Johnstone, *Der. Anaesthesist*, **9**, 114 (1960); (e) G. deCastro and P. Mundeleer, *Agressologie*, **1**, 511 (1960); (f) B. J. Muir, V. Evans, and J. J. Mulcahy, *Brit. J. Anesthesia*, **33**, 51 (1961).
(6) J. Davoll and D. H. Laney, *J. Chem. Soc.*, 2124 (1956).
(7) N. Kursanov, *J. Russ. Phys. Chem. Soc.*, **38**, 1295 (1907); *Chem. Abstr.*, **1**, 2093 (1907).

phenylcyclohexane followed by the chemical reduction of the resulting nitro compound to the amine. Since this method is not suitable for synthesis of large amounts of the primary amine, various other methods were investigated.

The reaction of olefins of the type RR'C=CHR'' with hydrogen cyanide or nitriles in the presence of strong acids has been reported by Ritter, *et al.*,[8] to yield acylated *t*-carbinamines (RR'CNHAcCH$_2$R''). The reaction of phenylcyclohexene with hydrogen cyanide in strongly acidic media for 2 hr. yielded a formamide which on acid hydrolysis produced an amine hydrochloride whose spectral data and analysis were in agreement with structure IIc (Ar = phenyl). However, this compound melted at 247–248° as compared with the literature value[7] of 230–230.5°; furthermore, the melting points of two cited derivatives exhibited sufficient variance with the ones obtained by us to warrant the elaboration of an alternate unambiguous synthesis of 1-phenylcyclohexylamine. The compound prepared by the alternate route (method F) was identical in all respects with the one obtained prepared from



phenylcyclohexene. Recently, Cristol, *et al.*,[9] reported the isolation of the amine as its benzoyl derivative *via* a modified Ritter reaction.

Pharmacology.—The 1-arylcyclohexylamines were evaluated in a variety of biological systems. The cataleptic activity was determined by the method of Chen[10] by intramuscular injection into pigeons and notation of the loss of righting reflex without head drop. Compounds **1, 9, 13, 15, 16, 28, 29, 41, 42, 48,** and **51** represent the most active members of the series and exhibit maximum activity at doses ranging from 6–25 mg./kg.

The antitonic extensor properties of the compound were studied in the mouse employing a modification of the electroshock method of Toman, *et al.*[11] A current of 24 mamp. was applied for 0.2 sec. through clips on the ears. The end point was the abolishment of the extensor component of the convulsion. The test compounds were dissolved in water and administered intraperitoneally. Those compounds which exhibited a PD_{50} (the dose/kg. that protects 50% of the animals) of 3 to 12.5 mg./kg. were **1**,[12] **3, 13, 18–21, 24, 27–31, 47,** and **48**.

Experimental[13]

1-Piperidinocyclohexanecarbonitrile.[1]—Cyclohexanone (64.8 g., 0.66 mole) was added to a solution of sodium bisulfite (75.6 g., 0.726 mole) in 250 ml. of water. To the cooled slurry of the bisulfite addition product was added a solution of KCN (47.2 g., 0.725 mole) and piperidine (56.9 g., 0.668 mole) in 200 ml. of water. This mixture was stirred and cooled overnight and then the product was filtered off, washed with water, and dried *in vacuo* at 30° to give 109.9 g. (86.6%) of material, m.p. 70–71.5° (lit.[1] m.p. 59°), b.p. 118° (2.5 mm.).

Anal. Calcd. for $C_{12}H_{20}N_2$: C, 74.95; H, 10.48. Found: C, 75.14; H, 10.29.

The **hydrochloride** was prepared using 2-propanolic HCl and after recrystallization from 2-propanol and cyclohexane melted at 226–228° (lit.[1] m.p. 217°).

Anal. Calcd. for $C_{12}H_{21}ClN_2$: C, 63.00; H, 9.25; Cl, 15.50. Found: C, 63.09; H, 9.39; Cl, 15.62.

The **amide**, prepared by hydrolysis with sulfuric acid, after recrystallization from ethanol melted at 103–105° (lit.[1] m.p. 91°).

Anal. Calcd. for $C_{12}H_{22}N_2O$: C, 68.52; H, 10.55. Found: C, 68.77; H, 10.57.

1-Arylcyclohexylamines of Type I (Method A). 1-(1-Phenylcyclohexyl)piperidine (a).—A solution of 1-piperidinocyclohexanecarbonitrile (39 g., 0.203 mole) in 130 ml. of isooctane was added to a refluxing solution of phenylmagnesium bromide, prepared from bromobenzene (79 g., 0.053 mole) and magnesium (12.3 g., 0.505 g.-atom) in 200 ml. of dry ether. The mixture was heated for 1 additional hr., 60 ml. of isooctane was added, and all the ether was distilled. The cooled reaction mixture was then hydrolyzed with 4 *N* HBr (175 ml.). The precipitate was filtered off and dissolved in 700 ml. of hot water. After extraction with isooctane to remove diphenyl, the aqueous solution was neutralized with K_2CO_3. The free base was separated by extraction with 70 ml. of isooctane. After charcoal filtration and distillation of solvent, the crude crystalline free base was washed twice with a total of 25 ml. of methanol to give 26.8 g. (54.2%) of colorless, crystalline product, m.p. 46–46.5°; the ultraviolet spectrum in 0.1 *N* HCl had λ_{max} 268.5 mμ ($E^{1\,cm}_{1\%}$ 9.7), 262 (13), 257.5 (11.2), 252 (7.9).

Anal. Calcd. for $C_{17}H_{25}N$: C, 83.89; H, 10.35; N, 5.76. Found: C, 83.94; H, 10.74; N, 5.98.

The **hydrochloride** was prepared using 2-propanolic HCl and was recrystallized from 2-propanol, m.p. 233–233.5°; the ultraviolet spectrum in ethanol had λ_{max} 269 mμ ($E^{1\,cm}_{1\%}$ 10.0), 262.5 (12.7), 258 (10.8), 254 (7.9).

Anal. Calcd. for $C_{17}H_{26}ClN$: C, 72.96; H, 9.37; Cl, 12.67. Found: C, 72.98; H, 9.24; Cl, 12.67.

(b).—A solution of cyclohexanone (98 g., 1 mole), piperidine (100 g., 1.17 moles), and *p*-toluenesulfonic acid monohydrate (2 g., 0.0105 mole) in 300 ml. of toluene was refluxed for 13 hr. using a Barrett water trap. A total of 19 ml. of water was obtained. The reaction mixture was diluted to 2 l. with dry toluene and treated with dry HBr until acidic. The slurry was added at once to a cold (5°) stirred solution of phenylmagnesium bromide, prepared from bromobenzene (236 g., 1.51 moles), magnesium (38 g., 1.56 g.-atoms), and 1 l. of dry ether. The temperature rose to 45° and the mixture was stirred for 30 min. further. After hydrolysis with 300 ml. of 48% aqueous HBr, there was obtained 189 g. (58%) of crude 1-(1-phenylcyclohexyl)-piperidine hydrobromide, m.p. 225–226°. The crude hydrobromide was basified and extracted with benzene. After treating with excess 2-propanolic HCl and diluting with ether, the hydrochloride was obtained (161 g.), m.p. 234–234.5°.

Type IIa Compounds (Method B). N-Cyclohexylidenethylamine (a).—To cyclohexanone (196 g., 2 moles), cooled to 0°, cold ethylamine (100 g., 2.21 moles) was added. An exothermic reaction occurred and the temperature rose to 23°. After standing in the cold for 2 hr., KOH pellets were added at intervals, and the aqueous basic layer was removed periodically for about 48 hr. The final oil layer after drying over fresh KOH pellets was distilled through a Vigreux column. Essentially pure product was obtained at 65–67° (15 mm.), $n^{25}D$ 1.4692, yield 150 g. (59.8%). This was of sufficient purity for use as an intermediate.

Anal. Calcd. for $C_8H_{15}N$: N, 11.18. Found: N, 10.45.

(b).—A solution of cyclohexanone (98 g., 1 mole) and ethylamine (56.4 g., 1.25 moles) in 400 ml. of petroleum ether was allowed to stand overnight at room temperature. The aqueous layer was removed and an additional 11 g. of ethylamine was added to yield 110 g. (88.1%), $n^{25.5}D$ 1.4673.

(8) J. J. Ritter and J. Kolish, *J. Am. Chem. Soc.*, **70**, 4048 (1948).

(9) H. Cristol, A. Laurent, and M. Mousseron, *Bull. Soc. Chim. France*, 2319 (1961).

(10) G. Chen, to be published, Parke, Davis and Co., Ann Arbor, Mich.

(11) J. E. P. Toman, E. A. Swinyard, and L. S. Goodman, *J. Neurophysiol.*, **9**, 231 (1946).

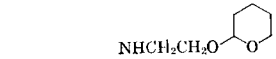
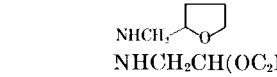
(12) G. Chen and B. Bohner, *Proc. Soc. Exptl. Biol. Med.*, **106**, 632 (1961).

(13) All melting points and boiling points are uncorrected. Melting points were obtained with a Fisher-Johns block. (These constants were determined before the Journals of the American Chemical Society announced the requirement of melting point corrections.)

TABLE I

1-AMINOARYLCYCLOHEXANES

Compd.	Ar	R	B.p. (mm.) and/or m.p., °C.	m.p. of HCl salt, °C.	Method	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1	C_6H_5	NC_5H_{10}[a]	108–109 (0.25) 45.5–46.5	233–233.5	A	$C_{17}H_{25}N\cdot HCl$	72.96	9.37	72.98	9.24
2	2-$CH_3C_6H_4$	NC_5H_{10}	127–130 (0.25)	208–209	A	$C_{18}H_{27}N\cdot HCl$	73.56	9.60	73.35	9.73
3	3-$CH_3C_6H_4$	NC_5H_{10}	64–66	...	A	$C_{18}H_{27}N$	83.98	10.57	83.84	10.74
4	4-$CH_3C_6H_4$	NC_5H_{10}	117–122 (0.25)	136–137	A	$C_{18}H_{27}N\cdot HCl$	73.56	9.60	73.38	9.66
5	2-ClC_6H_4	NC_5H_{10}	145 (0.55)	...	A	$C_{17}H_{24}ClN$	73.49	8.71	73.68	8.77
6	3-ClC_6H_4	NC_5H_{10}	89–90	222–224	A	$C_{17}H_{24}ClN\cdot HCl$	64.96	8.02	64.95	8.28
7	4-BrC_6H_4	NC_5H_{10}	136–138 (0.75) 47–48	133–135	A	$C_{17}H_{24}BrN\cdot HCl$	56.91	7.02	57.06	7.65
8	2-$CH_3OC_6H_4$	NC_5H_{10}	141–142 (0.3) 50–52	202–202.5	A	$C_{18}H_{27}NO\cdot HCl$	69.77	9.11	69.90	9.11
9	4-$CH_3OC_6H_4$	NC_5H_{10}	...	186–187	A	$C_{18}H_{27}NO\cdot HCl$	69.77	9.11	69.52	9.17
10	4-$C_6H_5OC_6H_4$	NC_5H_{10}	102–103	197–199	A	$C_{23}H_{29}NO\cdot HCl$	74.26	8.13	74.08	8.18
11	1-Naphthyl	NC_5H_{10}	169–171 (0.3)	235–237	A	$C_{21}H_{27}N\cdot HCl$	76.45	8.55	76.62	8.55
12	9-Fluorenyl	NC_5H_{10}	...	172–173	A[b]	$C_{29}H_{29}N\cdot HCl$	78.34	8.22	78.54	8.26
13	C_6H_5		114–123 (0.14)	235–237	A	$C_{18}H_{25}N\cdot HCl$	72.29	9.10	72.51	9.02
14	C_6H_5		135–137 (0.3) 68–69	187–189	A	$C_{18}H_{23}NO\cdot HCl$	78.34	9.45	78.54	9.51
15	C_6H_5		123–126 (0.2)	210–211	A	$C_{18}H_{25}N$	83.98	10.58	83.67	10.53
16	C_6H_5		126–130 (0.140)	...	A	$C_{19}H_{28}N$	84.07	10.73	84.23	10.89
17	C_6H_5		128–130 (0.13) 59–60	215–216	A	$C_{18}H_{25}N$	83.98	10.58	83.94	10.53
18	C_6H_5	$N(CH_3)_2$	120–125 (0.25)	164–165	C	$C_{14}H_{21}N\cdot HCl$	70.12	9.25	70.16	9.67
19	C_6H_5	$NCH_3(C_2H_5)$	105–108 (0.12)	194–195	C	$C_{15}H_{23}N\cdot HCl$	70.98	9.53	70.90	9.64
20	2-$CH_3C_6H_4$	$NCH_3(C_2H_5)$	82–88 (0.1)	158–160	C	$C_{16}H_{25}N$	83.06	10.89	83.22	11.00
21	3-$CH_3C_6H_4$	$N(CH_3)C_2H_5$	97–98 (0.1)	...	C	$C_{16}H_{25}N$	83.06	10.89	83.08	10.57
22	4-$CH_3OC_6H_4$	$N(CH_3)C_2H_5$	102–110 (0.1)	...	C	$C_{16}H_{25}NO$	77.68	10.19	77.44	9.52
23	C_6H_5		140–145 (2)	...	C	$C_{19}H_{32}N_2$	79.10	11.18	79.10	11.12
24	C_6H_5	$N(C_2H_5)_2$	102–107 (0.12)	...	D	$C_{16}H_{25}N$	83.06	10.89	82.88	10.66

25	4-$CH_3C_6H_4$	$N(C_2H_5)_2$	...	170–171	D	$C_{17}H_{27}N \cdot HCl$	72.43	10.01	72.66	9.90
26	4-ClC_6H_4	$N(C_2H_5)_2$	102–112 (0.1)	177–179	D	$C_{16}H_{24}ClN \cdot HCl$	63.57	8.34	63.27	8.19
27	C_6H_5	$NHCH_3$	76–78 (0.15)	185–186	B	$C_{13}H_{19}N \cdot HCl$	69.16	8.93	69.09	8.90
28	C_6H_5	NHC_2H_5	...	236–237	B	$C_{14}H_{21}N \cdot HCl$	70.12	9.25	70.41	9.08
29	C_6H_5	NHC_3H_7-*n*	...	203–204	B	$C_{15}H_{23}N \cdot HCl$	70.98	9.53	71.08	9.43
30	C_6H_5	NHC_3H_7-*i*	99–101 (0.9)	234–235	B	$C_{15}H_{23}N \cdot HCl$	70.98	9.53	71.44	9.82
31	C_6H_5	$NHCH_2CH{=}CH_2$	120–123 (3)	208–209	B	$C_{15}H_{21}N$	83.66	9.83	83.48	9.98
32	C_6H_5	NHC_5H_{11}-*n*	109–112 (0.3)	175–176	B	$C_{17}H_{25}N \cdot HCl$	72.43	10.01	72.24	10.05
33	C_6H_5	$NHCH_2C_6H_5$	163–164 (0.32)	226–227	B	$C_{19}H_{23}N$	84.71	10.10	84.56	9.82
34	C_6H_5	$NHCH_2CH_2CH_2N(CH_3)_2$	138–139 (3)	236–237	B	$C_{17}H_{28}N_2 \cdot 2HCl$	61.26	9.09	60.95	9.07
35	C_6H_5	$NHCH_2CH_2N(C_2H_5)_2$	129–131 (3)	230–231	B	$C_{18}H_{30}N_2 \cdot 2HCl$	62.35	9.30	62.09	9.25
36	C_6H_5		150–155 (0.350)	200–201	B	$C_{18}H_{28}N_2O$	74.95	9.78	74.69	9.60
37	C_6H_5		158–160 (0.09)	...	B	$C_{19}H_{29}NO_2$	75.20	9.63	75.25	9.59
38	C_6H_5	$NHCH_2CH_2OH$	140–145 (0.1)	182–183	E	$C_{14}H_{21}NO \cdot HCl$	65.73	8.67	65.66	8.51
39	C_6H_5		170–175 (0.12)	...	B	$C_{20}H_{31}NO_2$	75.66	9.81	75.71	9.83
40	C_6H_5	$NHCH_2C(OH)CH_3$	140–143 (0.11)	198–199	E	$C_{15}H_{23}NO \cdot HCl$	66.77	8.97	66.66	9.00
41	C_6H_5	$NHCH_2CH_2OCH_3$	102–105 (1)	201–202	B	$C_{15}H_{23}NO$	77.20	9.93	77.37	9.87
42	C_6H_5	$NHCH_2CH_2CH_2OCH_3$	142–146 (2.5)	192–193	B	$C_{16}H_{25}NO \cdot HCl$	67.70	9.23	67.53	8.97
43	C_6H_5	$NH(CH_2)_5OCH_3$	142–144 (0.09)	140–141	B	$C_{18}H_{29}NO \cdot HCl$	69.32	9.70	69.56	9.70
44	C_6H_5	$NH(CH_2)_3OCH(CH_3)_2$	132–136 (0.1)	137–138	B	$C_{18}H_{29}NO \cdot HCl$	69.32	9.70	69.18	9.64
45	C_6H_5	$NH(CH_2)_3SCH_3$	...	188–190	B	$C_{16}H_{25}NS \cdot HCl$	64.07	8.74	63.85	8.90
46	C_6H_5		153–158 (0.15)	179–180	B	$C_{17}H_{25}NO$	78.72	9.71	78.62	9.70
47	C_6H_5	$NHCH_2CH(OC_2H_5)_2$	149–150 (0.15)	...	B	$C_{18}H_{29}NO_2$	74.18	10.03	73.91	10.13
48	2-$CH_3C_6H_4$	$NHCH_3$	...	228–229	B	$C_{14}H_{21}N \cdot HCl$	70.12	9.25	70.44	9.57
49	3-$CH_3C_6H_4$	$NHCH_3$	...	215–216	B	$C_{14}H_{21}N \cdot HCl$	70.12	9.25	70.55	9.36
50	2-$CH_3C_6H_4$	NHC_2H_5	121–125 (0.15)	223–224	B	$C_{15}H_{23}N \cdot HCl$	70.98	9.53	70.63	9.52
51	3-$CH_3C_6H_4$	NHC_2H_5	150–152 (0.2)	236–237	B	$C_{15}H_{23}N$	82.89	10.67	83.19	10.65
52	4-$CH_3C_6H_4$	NHC_2H_5	134–135 (0.1)	209–210	B	$C_{15}H_{23}N$	82.89	10.67	82.85	10.79
53	3-$CH_3C_6H_4$	$NHCH_2C_6H_5$	137–140 (0.75)	221–222	G	$C_{20}H_{25}N \cdot HCl$	76.04	8.30	76.18	8.33
54	3-ClC_6H_4	NHC_2H_5	98–103 (0.13)	271–272	B	$C_{14}H_{20}ClN \cdot HCl$	61.58	7.75	61.37	7.94
55	4-ClC_6H_4	NHC_2H_5	111–113 (0.2)	259–260	B	$C_{14}H_{20}ClN \cdot HCl$	61.58	7.75	61.38	7.79
56	4-$OCH_3C_6H_4$	NHC_2H_5	90–92 (0.05)	187–188	B	$C_{15}H_{23}NO \cdot HCl$	66.77	8.97	66.89	8.98
57	4-$N(C_2H_5)_2C_6H_4$	NHC_2H_5	131–137 (0.025)	...	B	$C_{18}H_{30}N_2$	78.77	11.02	78.67	10.91
58	3,4-di-$OCH_3C_6H_3$	NHC_2H_5	...	232–233	B	$C_{16}H_{25}NO_2 \cdot HCl$	64.09	8.74	64.10	8.90
59	C_6H_5	NH_2	92–97 (1)	247–248	F[c]	$C_{12}H_{17}N \cdot HCl$	68.07	8.58	68.14	8.62
60	3-$CH_3C_6H_4$	NH_2	...	126–128 (acetate)	G	$C_{13}H_{19}N \cdot CH_3COOH$	72.25	9.36	71.89	9.37

[a] NC_5H_{10} represents the piperidino radical. [b] Fluorene was metallated with phenyllithium followed by magnesium bromide to form fluorenylmagnesium bromide. [c] Also prepared by a Ritter reaction from phenylcyclohexene.

N-Ethyl-1-phenylcyclohexylamine.—Phenyllithium was prepared from lithium ribbon (22.2 g., 3.20 g.-atoms) and bromobenzene (251 g., 1.6 moles) in 1 l. of diethyl ether. N-Cyclohexylidenethylamine (100 g., 0.8 mole) in 320 ml. of diethyl ether was added in 30 min., and the reaction mixture was heated at reflux for 1 hr. After hydrolysis of the reaction mixture with water, the ether was distilled, and the residue was distilled *in vacuo*. Three preparations of the base gave yields of 51–60%.

One modification of this procedure in which the ether layer was extracted with cold 3 *N* HCl followed by regeneration of the free base gave a 50.3% yield of base distilling at 69–71° (0.04 mm.), $n^{25.5}$D 1.5285. The ultraviolet spectrum in 0.1 *N* HCl showed λ_{max} 268 mμ ($E^{1cm}_{1\%}$ 11.6), 261 (15.3), 257 (15.15), 251 (12.0).

Anal. Calcd. for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 83.01; H, 10.16; N, 6.64.

The **hydrochloride** was prepared from the base in a yield of 85%, m.p. 240–242°, pK_a' = 9.7 in 50% methanol.

Anal. Calcd. for $C_{14}H_{22}ClN$: C, 70.12; H, 9.25; Cl, 14.79; N, 5.84. Found: C, 69.95; H, 9.25; Cl, 14.67; N, 5.98.

Type IIb Compounds (Method C). N-Cyclohexylidenemethylamine.—To cyclohexanone (196 g., 2.0 moles) cooled to −3° was added liquid methylamine (64 g., 2.2 moles). The solid mixture was warmed to form a solution, and then KOH pellets were added. After two further additions of KOH pellets and removal of the aqueous phase at 24-hr. intervals, the product was distilled *in vacuo*. The oil distilled at 45–46° (9–10 mm.) as a colorless liquid with a yield of 165 g. (74.3%). This product was used directly in the next reaction.

N-Methyl-1-phenylcyclohexylamine.—Phenyllithium was prepared from lithium wire (36.4 g., 5.2 g.-atoms) and bromobenzene (376 g., 2.4 moles) in a total of 1900 ml. ether. To this was added N-cyclohexylidenemethylamine (165 g., 1.48 moles) in 300 ml. of anhydrous ether during 45 min. After 3 hr. at reflux, 1.5 l. of water was added, and the ether layer was separated, water washed, and dried ($MgSO_4$). After removal of ether, the residue was distilled. There was obtained 298 g. (65%) of product, b.p. 76–78° (150 μ). Infrared analysis showed no absorption characteristic of the C=N bond.

The **hydrochloride** was prepared by treating the base in ether with HCl, m.p. 185–186°.

Anal. Calcd. for $C_{13}H_{20}ClN$: C, 69.16; H, 8.93. Found: C, 69.09; H, 8.90.

N,N-Dimethyl-1-phenylcyclohexylamine.—N-Methyl-1-phenylcyclohexylamine (188 g., 0.993 mole) and formic acid (102 g., 2.22 moles) were mixed, and to the solution was added 87 g. of 38% formaldehyde. A vigorous exothermic reaction took place. The reaction mixture was then warmed on a steam bath for 1 hr., basified with 5 *N* NaOH, and extracted with ether. After drying the solution and removing the ether, the residue was distilled *in vacuo*. The product was obtained in a yield of 168 g. (83%), b.p. 96–98° (50–60 μ). The liquid readily crystallized, m.p. 42–44°.

The **hydrochloride** was prepared by dissolving the base in ether (500 ml.) and adding 2-propanolic HCl to afford 120 g. after one recrystallization from 2-propanol.

Ultraviolet assay indicated that this was the mono-2-propanolate. Recrystallization from dioxane of a sample of the hydrochloride gave a colorless solid.

Anal. Calcd. for $C_{14}H_{22}ClN$: C, 70.12; H, 9.25. Found: C, 70.16; H, 9.67.

Type IIb Compounds (Method D). N-Acetyl-N-ethyl-1-phenylcyclohexylamine.—N-Ethyl-1-phenylcyclohexylamine (7.4 g., 0.036 mole) was dissolved in 30 ml. of acetic acid and 5 g. of acetic anhydride. After heating on the steam bath for 1 hr., the solution was concentrated in a rotating evaporator. A small sample of the residue gave crystals from trimethylpentane, m.p. 55–56°.

Anal. Calcd. for $C_{16}H_{23}NO$: N, 5.71. Found: N, 6.00.

N,N-Diethyl-1-phenylcyclohexylamine.—The bulk of the residue from above (7.1 g.) was dissolved in 50 ml. of benzene and washed with dilute HCl and then dilute $NaHCO_3$. The solution was dried and added dropwise to lithium aluminum hydride (4 g.) in 400 ml. of anhydrous ether. After decomposing with water and NaOH, the mixture was filtered and the solvent was removed. The residue was distilled *in vacuo* to give 4.1 g., b.p. 102–107° (120 μ).

Anal. Calcd. for $C_{16}H_{25}N$: C, 83.06; H, 10.89. Found: C, 82.89; H, 10.66.

Type IId Compounds (Method E). 2-Tetrahydropyranyloxy-β-ethylamine.—To a suspension of lithium aluminum hydride (24 g., 0.6 mole) in 2 l. of dry ether was added 2-cyanomethoxytetrahydropyran[14] (125 g., 0.885 mole) dissolved in ether (125 ml.). After heating at reflux for 3 hr., the mixture was decomposed with water and NaOH. After filtration and removal of solvent, the residue was distilled *in vacuo* to give 74 g. (54%), b.p. 53–58° (0.3 mm.).

Anal. Calcd. for $C_7H_{15}NO_2$: C, 57.90; H, 10.41. Found: C, 57.92; H, 10.50.

N-(β-Tetrahydropyranyloxy)ethyl-1-phenylcyclohexylamine.—A solution of cyclohexanone (57 g., 0.58 mole) and 2-tetrahydropyranyloxy-β-ethylamine (74 g., 0.51 mole) in 250 ml. of benzene was heated at reflux with a water trap until all water was removed. The benzene was distilled off and replaced with dry ether. A phenyllithium solution, prepared from lithium (18.2 g., 2.62 g.-atoms) and bromobenzene (186 g., 1.19 moles) in 800 ml. of dry ether, was added and the reaction mixture heated at reflux for 1 hr. After decomposing with water, the ether layer was dried and the solvent was distilled. The residue was distilled *in vacuo* to give 89 g. (59%), b.p. 158–160° (90 μ).

Anal. Calcd. for $C_{19}H_{29}NO_2$: C, 75.20; H, 9.63. Found: C, 75.25; H, 9.59.

N-(β-Hydroxyethyl)-1-phenylcyclohexylamine. A mixture of N-(β-2-tetrahydropyranyloxy)ethyl-1-phenylcyclohexylamine (30.3 g., 0.1 mole) and 250 ml. of 10% acetic acid was heated at reflux for 30 min. After removal of most of the water, 200 ml. of 5 *N* NaOH was added. The product was isolated by ether extraction, and after the solvent was removed, the residue was distilled *in vacuo*. A viscous liquid (20 g.) was obtained, b.p. 140–145° (100 μ).

Anal. Calcd. for $C_{14}H_{21}NO$: N, 6.40. Found: N, 6.20.

The **hydrochloride** after one recrystallization from methanol and ether melted at 182–183°.

Anal. Calcd. for $C_{14}H_{22}ClNO$: C, 65.73; H, 8.67. Found: C, 65.56; H, 8.51.

Type IIc Compounds (Method F). 1-Phenylcyclohexanecarbonitrile.[15] A mixture of phenylacetonitrile (222 g., 1.9 moles) and 1,5-dibromopentane (400 g., 1.71 moles) was added in 6 hr. to sodamide (593 g., 7.54 moles) in 4.5 l. of diethyl ether at reflux temperature. The reaction mixture was heated at reflux overnight, and 1.6 l. of water was added in 2.5 hr. at 21–24° with cooling. The mixture was then heated at reflux for 1 hr. and cooled. After filtration and separation of the aqueous layer, the ether layer was washed with 1 l. of water and 1 l. of 3 *N* HCl. The solvent was distilled and afforded 234 g. (72.8%) of crude product. Fractional distillation afforded a 62% yield of pure product, b.p. 102° (0.10 mm.), n^{26}D 1.5323; lit.[15] b.p. 110–115° (0.7 mm.), n^{25}D 1.5327. The ultraviolet spectrum in ethanol showed λ_{max} 263 mμ ($E^{1\%}_{1cm}$ 7.94), 257 (10.22).

An identical preparation in which the mixture of phenylacetonitrile and 1,5-dibromopentane was added in 70 min. afforded only 130 g. (40.2%) of pure distilled product.

Anal. Calcd. for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.39; H, 8.36; N, 7.52.

1-Phenylcyclohexanecarboxamide.[15]—A mixture of 1-phenylcyclohexanecarbonitrile (130 g., 0.7 mole), 415 g. of trifluoroacetic acid, and 59.5 g. of H_2SO_4 was heated at reflux for 16 hr. and then poured on 500 g. of ice. A tan-colored crystalline solid formed. The solid was slurried with water, aqueous Na_2CO_3, and water until neutral. The crude product after drying weighed 121 g. (85.5%). Recrystallization from isooctane afforded 72.3 g. (50.8%) of amide, m.p. 85–88°, suitable for use as an intermediate.

1-Phenylcyclohexylamine. A. From 1-Phenylcyclohexanecarboxamide.—To a cooled solution of 198 g. of KOH in 1 l. of water was added 18 ml. of bromine, and the mixture was cooled further to 7°. 1-Phenylcyclohexanecarboxamide (67.3 g., 0.331 mole) was added at once and the mixture was held at 3–9° for 90 min. with stirring. It was extracted three times with 200 ml. of diethyl ether. Concentrated HCl (300 ml.) was heated to 50° and the extracts were added as obtained. The reaction mixture was then heated to 110° in 90 min. After cooling to 85°, 210 g. of NaOH in 900 ml. of water was added in 15 min. After cooling and extracting with 600 ml. of ether, the solution was dried over NaOH pellets. The ether was distilled to give a residue of crude amine weighing 46.4 g. (89.3%).

(14) (a) A. W. Weston, *J. Am. Chem. Soc.*, **68**, 2345 (1946); (b) H. E. Lyle and G. G. Lyle, *ibid.*, **74**, 4059 (1952).

(15) F. Case, *ibid.*, **56**, 715 (1934).

The **hydrochloride** was prepared in a yield of 47.3 g. (68%), m.p. 247–248°; ultraviolet analysis in 0.1 *N* HCl showed λ_{max} 267 mμ ($E^{1\,cm}_{1\%}$ 5.91), 260.5 (8.97), 256 (9.98), 250.5 (7.39).

Anal. Calcd. for $C_{12}H_{18}ClN$: C, 68.07; H, 8.58; N, 6.62. Found: C, 68.14; H, 8.62; N, 6.64.

The base was treated with phenyl isothiocyanate to yield 1-phenyl-3-(1-phenylcyclohexyl)-2-thiourea, m.p. 168–169° (lit.[7] m.p. 156°).

Anal. Calcd. for $C_{19}H_{22}N_2S$: C, 73.50; H, 7.14. Found: C, 73.61; H, 7.29.

In addition, 1-phenylcyclohexylamine formed an acetate salt melting at 144–145° (lit.[7] m.p. 155°).

B. From 1-Phenylcyclohexene.—To a mixture of 1-phenylcyclohexene (15.8 g., 0.1 mole), 50 ml. of dibutyl ether, and NaCN (12.2 g., 0.25 mole) at 40° was added in 1 hr. 30 ml. of H_2SO_4. After stirring for an additional hour, the reaction mixture was poured into water and extracted with ether. The ether and dibutyl ether were distilled *in vacuo*, 30 ml. of HCl was added to the residue, and the mixture refluxed for 3 hr. The aqueous layer was separated, made alkaline with NaOH, and then extracted with ether.

The **hydrochloride** was prepared by adding a solution of HCl in 2-propanol, and the cloudy solution was evaporated to dryness. To the residue was added 20 ml. of acetone, and the crude product was recrystallized twice from methanol and ether to give needles, m.p. 247–248°. A mixture melting point of this hydrochloride with that prepared from 1-phenylcyclohexanecarboxamide showed no depression. The infrared spectra (KBr disk) were identical.

1-Phenylcyclohexyl Isocyanate.—In a separate preparation from 43.8 g. of 1-phenylcyclohexanecarboxamide, the intermediate 1-phenylcyclohexyl isocyanate was isolated by evaporation of the ether extracts. After separation of 4.7 g. of colorless crystalline material, presumably the urea, a yellow oil was obtained. This was distilled through a Vigreux column *in vacuo* to give 27.5 g. (63.5%) of colorless oil, b.p. 101–102° (0.25–0.40 mm.), $n^{27}D$ 1.5341; the ultraviolet spectrum in absolute ethanol had λ_{max} 263 mμ ($E^{1\,cm}_{1\%}$ 8.6), 257 (11.8), 252 (10.4), and 247 (8.1).

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51. Found: C, 77.72; H, 7.51.

Type IIc Compounds (Method G). 1-(*m*-Tolyl)-N-benzylcyclohexylamine.—To a solution of *m*-tolyllithium [from *m*-bromotoluene (171 g., 1.0 mole), lithium (14 g., 2.0 g.-atoms), and 500 ml. of anhydrous diethyl ether] was added a solution of N-benzylcyclohexylideneamine [(187 g., 1.0 mole) prepared by refluxing a solution of benzylamine and cyclohexanone in toluene with a water trap] in 500 ml. of anhydrous diethyl ether over a period of 1 hr. at reflux. The reaction mixture was heated at reflux for an additional 3 hr.

After cooling in an ice bath, the reaction mixture was hydrolyzed with 300 ml. of water. The organic layer was separated and the aqueous layer was extracted with 100 ml. of benzene. The combined organic layers, after drying, were distilled to remove solvent, and the residue was distilled *in vacuo*. After removal of a forerun of N-benzylcyclohexylidineamine, there was obtained 72.5 g. of 1-(*m*-tolyl)-N-benzylcyclohexylamine (26% yield), $n^{26}D$ 1.5687, b.p. 137–140° (75 μ); the ultraviolet spectrum in 0.1 *N* HCl showed λ_{max} 286 mμ ($E^{1\,cm}_{1\%}$ 45.2), 274 (45.8), 267 (47.2), and 257 (50.4).

Anal. Calcd. for $C_{20}H_{25}N$: C, 85.96; H, 9.02; N, 5.01. Found: C, 85.76; H, 9.34; N, 5.13.

The **hydrochloride** was prepared using 2-propanolic hydrogen chloride, m.p. 221–222°.

Anal. Calcd. for $C_{20}H_{26}ClN$: C, 76.04; H, 8.30; Cl, 11.23. Found: C, 76.18; H, 8.33; Cl, 11.32.

1-(*m*-Tolyl)cyclohexylamine.—1-(*m*-Tolyl)-N-benzylcyclohexylamine (30 g.) was reduced catalytically in glacial acetic acid using 20% palladium on carbon at an initial pressure of 3.5 kg./cm.² (50 p.s.i.). After removal of the catalyst, the filtrate was concentrated *in vacuo* to give a viscous liquid. On standing, this material crystallized. Recrystallization from 2-propanol and ether gave 8.0 g. of 1-(*m*-tolyl)cyclohexylamine acetate. Further recrystallization from 2-propanol gave colorless needles, m.p. 126–128°; the ultraviolet spectrum in 0.1 *N* HCl showed λ_{max} 272 mμ ($E^{1\,cm}_{1\%}$ 17.4), 265 (19.6).

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.63. Found: C, 71.89; H, 9.37; N, 5.56.

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Structures Related to Morphine. XXVIII.[1] Alternative Syntheses of α- and β-2,9-Dimethyl-2′-hydroxy-5-propyl-6,7-benzomorphan

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α- and β-2,9-dimethyl-2′-hydroxy-5-propyl-6,7-benzomorphans (VI and V, respectively) have been synthesized from either 7-methoxy-β-tetralone or 3-methyl-4-propylpyridine and degraded to 7-methoxy-2-methyl-1-propylnaphthalene. Certain reactions in these sequences can be stereo regulated, some to only a limited extent. The rate of methiodide formation and infrared absorption data have served to distinguish V and VI. Both isomers (particularly V) are potent analgetics.

In a "summary" paper[3] on 6,7-benzomorphans, the α-2,9-dimethyl-2′-hydroxy-5-propyl analog (VI) was included but only limited chemical and pharmacological data were then available. The present report is concerned with the synthesis of VI and the β-diastereoisomer (V) by two different routes (some of the reactions being stereo regulatable) along with analgetic (mice) and addiction (monkey) data.

When 1,3-dimethyl-2-(*p*-methoxybenzyl)-4-propyl-1,2,5,6-tetrahydropyridine (IV), prepared from 1,3-dimethyl-4-propylpyridinium iodide by a method described previously[3,4] for homologous series, was cyclized with 48% hydrobromic acid at 140–150° or with 85% phosphoric acid at 180°, a 40–50% yield of α-benzomorphan (VI) was obtained. However, contrary to previous experience,[3] no crystalline β-base (V) or salts

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