

peutic ratios are compared to those of pentobarbital or phenobarbital.

Preliminary structure-activity correlations led us to make the following general statements. (1) The nature of the N-substituent is critical. One-carbon interruption between the aryl moiety and the nitrogen atom as well as alkyl branching of the α -carbon are prerequisites for sustaining hypnotic activity. Lengthening of the side chain to include two carbon atoms, with or without branching (*i.e.*, **46** and **47**), or omission of branching, *à la* **45**, or direct attachment of the aryl group upon the nitrogen (**44**), leads to total loss of hypnotic properties. (2) Differences in hypnotic potency among the various esters are relatively minor. The presence of the ester moiety *per se* is essential;

the corresponding carboxylic acids are totally inactive. A detailed pharmacological study, including test results obtained in other animals, will be published elsewhere.

Acknowledgment.—We are indebted to Messrs. T. Van Offenwert and A. Knaeps for the preparation of a number of starting materials and to Messrs F. Sels and W. Verkest for analytical determinations reported herein. Pharmacological assistance was rendered by Mr. F. Leenaerts. We also extend our thanks to Dr. C. van de Westeringh for his participation in fruitful chemical discussions during the course of this work. Financial support of the "Instituut tot Aanmoediging van het Wetenschappelijk Onderzoek in Nijverheid en Landbouw" is gratefully acknowledged.

Hypocholesteremic Agents. III.¹ Basic Carbinols and Related Compounds

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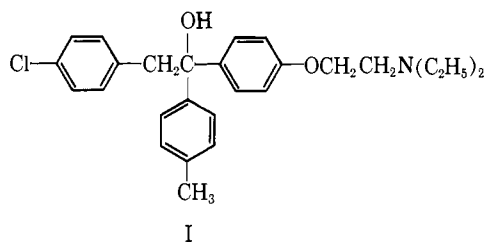
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A series of 58 basic carbinols and related compounds has been synthesized, mostly by means of the Grignard reaction, and examined for hypocholesteremic activity. One compound, α -[4-(2-diethylaminoethoxy)phenyl]- α -phenyl-5-acenaphthenemethanol, proved to be considerably more potent than triparanol in both rats and mice.

Much effort in recent years has been expended in the search for chemical agents which will significantly lower the blood cholesterol level of hypercholesteremic individuals. The rationale behind use of such drugs is the belief, not conclusively proven, that formation of atherosclerotic plaques is directly connected to the amount of cholesterol in the blood.^{2,3} Although a number of drugs are known to possess hypocholesteremic activity, none are entirely satisfactory.^{3,4} In 1959, triparanol was introduced for this purpose, and both animal and clinical studies indicate it to be both effective and consistent in its activity.^{5,6} It was soon discovered, however, that, as the level of cholesterol is reduced, the level of its biogenetic precursor, desmosterol, is increased and total sterol concentration of the plasma is not reduced as much as determinations of cholesterol would seem to indicate.^{2,3,6} A further possible disadvantage of triparanol is its lack of potency. A typical dose for human patients is 250 mg. daily.⁶ For drugs which are given over long periods of time, it might be advantageous to be able to give one effective at a lower dose. This work, then, was undertaken for two reasons; first, to find a drug similar to triparanol effective at a dose of no more than 50 mg./

day, and, second, one which would give a better reduction in total sterols.

Chemically, triparanol (I) is a derivative of 1,1,2-triphenylethanol. As such, there are many possible modifications which might lead to interesting struc-



ture-activity relationships. In a previous publication,⁷ we established that the 4-(2-(diethylaminoethoxy)phenyl) group may be replaced by a pyridine ring and activity maintained. The most potent compound of that series is 1,1-diphenyl-2-(4-pyridyl)ethanol. Its potency is about the same as that of I. Investigation of pyridine derivatives is continued in this paper, and modifications of the diethylaminoethoxy side chain have been studied extensively. Triarylmethanol homologs have also been investigated, as has replacement of benzene rings with polynuclear ring systems. In addition, a group of tetrahydrofuran derivatives and some ethylene derivatives has been synthesized.

Chemistry.—Four general methods were used to obtain the carbinols (IV, VI, IX, and XI), ethers, and ethylene derivatives described in Table I.

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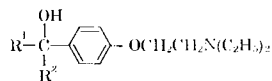
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TABLE I
CARBINOLS

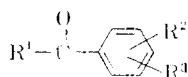
Compd.	R ¹	R ²	R ³	Method	B.p., °C. (mm.)	M.p., °C.	Formula	% C		% H		% N	
								Calcd.	Found	Calcd.	Found	Calcd.	Found
1	H	H	4-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O	A ^c	204-208 (0.25)	78-80	C ₂₀ H ₂₆ ClNO ₂	69.05	68.97	7.53	7.59	4.02	3.97
2	CH ₃	H	4-(CH ₃) ₂ NCH ₂ CH ₂ O	A	202-203 (1.3)	108-109	C ₁₉ H ₂₄ ClNO ₂	68.35	68.42	7.25	7.19		
3	ClH ₃	H	2-(CH ₃) ₂ NCH ₂ CH(CH ₃)O	A	210 (0.55)		C ₂₀ H ₂₆ ClNO ₂	69.05	69.01	7.53	7.28		
4	CH ₃	H	3-(CH ₃) ₂ NCH ₂ CH(CH ₃)O	A	208-209 (0.7)		C ₂₀ H ₂₆ ClNO ₂	69.05	69.21	7.53	7.54		
5	CH ₃	H	4-(ClH ₃) ₂ NCH ₂ CH(CH ₃)O	A	220 (1.8)		C ₂₀ H ₂₆ ClNO ₂	69.05	69.18	7.53	7.57		
6	CH ₃	4-CH ₃	2-(CH ₃) ₂ NCH ₂ CH(CH ₃)O	A	210 (1.6)		C ₂₁ H ₂₈ ClNO ₂	69.77	69.85	7.81	8.12		
7	CH ₃	3-CH ₃	4-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O	A	230-235 (1.8)		C ₂₂ H ₃₀ ClNO ₂	70.29	70.21	8.10	7.96		
8	CH ₃	3-CH ₃ O	4-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O	A ^b	191-197 (0.08)		C ₂₂ H ₃₀ ClNO ₃	67.41	67.40	7.71	7.75	3.57	3.55
9	CH ₃	2,5-(CH ₃) ₂	4-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O	A	234 (1.2)		C ₂₃ H ₃₂ ClNO ₂	70.84	71.08	8.27	8.10		
10	CH ₃	3,5-(CH ₃) ₂	4-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O	A	235 (1.3)		CH ₂₃₃₂ ClNO ₂	70.84	71.52	8.27	8.45		
11	C ₂ H ₅	H	3-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O	A	223 (1.7)		C ₂₂ H ₃₀ ClNO ₂	70.29	70.00	8.10	8.10		
12	C ₂ H ₅	H	4-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O	A ^c	225 (0.6)		C ₂₂ H ₃₀ ClNO ₂	70.29	70.28	8.10	7.79		
13	C ₂ H ₅	2-CH ₃	3-(CH ₃) ₂ N	A	190-196 (1.5)		C ₁₉ H ₂₄ ClNO	71.79	71.64	7.61	7.57		
14	<i>n</i> -C ₃ H ₇	H	4-(CH ₃) ₂ NCH ₂ CH(CH ₃)O	A	237 (1.3)		C ₂₂ H ₃₀ ClNO ₂	70.29	69.98	8.10	7.95		
15	CF ₃	H	4-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O	A	160-175 (0.7)		C ₂₁ H ₂₈ ClF ₃ NO ₂	60.64	60.91	6.05	5.89		
16	<i>d</i>			A	222-230 (0.0)	173-175 ^c	C ₂₃ H ₃₀ ClNO ₂ ·HCl	66.95	66.63	6.97	7.29		
17	C ₆ H ₅	H	4-(CH ₃) ₂ N	A ^f		134-136	C ₂₂ H ₂₂ ClNO	75.09	75.38	6.30	6.09		
18	C ₆ H ₅	H	4-(C ₂ H ₅) ₂ NCOC ₂ H ₅ O	A		155-158	C ₂₆ H ₂₈ ClNO ₃	71.30	71.68	6.44	6.53		
19	C ₆ H ₅	H	4-[(C ₂ H ₅) ₂ NCH ₂] ₂ CHO	A	225-235 (0.4)		C ₃₁ H ₄₀ ClN ₂ O ₂	73.12	73.58	8.07	8.23	5.51	5.20
20	C ₆ H ₅	4-CH ₃ O	2-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O	A		132-134 ^d	C ₂₇ H ₃₂ ClNO ₃	71.42	71.24	7.10	7.19	3.08	3.00
21	C ₆ H ₅	4-CH ₂ =CHCH ₂ O	2-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O	A		135-137	C ₂₉ H ₃₄ ClNO ₃	72.57	72.99	7.09	7.40	2.92	2.80
22	C ₆ H ₅	4- <i>n</i> -C ₁₂ H ₂₅ O	2-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O	A		115-117	C ₃₈ H ₅₄ ClNO ₃	75.06	74.73	8.99	8.93	2.30	2.60
23	C ₆ H ₅	3-CH ₃	4-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O	A		97-98	C ₂₇ H ₃₂ ClNO ₂	74.04	73.96	7.37	7.20		
24	C ₆ H ₅	3-Cl	4-(CH ₃) ₂ NCH ₂ CH(CH ₃)O	A		118-119 ^e	C ₂₅ H ₂₇ Cl ₂ NO ₂	67.56	67.66	6.12	6.02		
25	2-Thienyl			B		166-167 ^c	C ₂₄ H ₂₇ NO ₂ ·HCl	66.08	66.09	6.75	6.93	3.35	3.58
26	4-CF ₃ C ₆ H ₄			C	202-201 (0.35)		C ₂₆ H ₂₈ F ₃ NO ₂	70.42	70.47	6.32	6.75	3.16	3.35
27	4-C ₆ H ₅ C ₆ H ₄			C		118-121 ^d	C ₃₁ H ₃₃ NO ₂	82.45	82.72	7.37	7.23	3.10	2.78
28	4-C ₆ H ₅ OC ₆ H ₄			C		154-156 ^d	C ₃₁ H ₃₃ NO ₃ ·HCl	73.81	73.84	6.80	6.85	2.78	2.83
29	5-Acenaphthenyl			B ^e , C ^f		96-98 ^g	C ₃₀ H ₃₃ NO ₂	82.45	82.46	7.37	7.46	3.10	3.11
30	9-Phenanthryl			C		158-159 ^g	C ₃₃ H ₃₃ NO ₂	83.37	83.41	6.95	7.33	2.95	2.93
31	2-Pyridyl			B	220-225 (0.3)		C ₂₁ H ₂₅ N ₂ O ₂	76.57	76.33	7.49	7.68	7.44	7.35



	R ¹	R ²										
32	4-FC ₆ H ₄	CH ₃	B			C ₂₀ H ₂₆ FNO ₂	72.49	72.51	7.91	7.77	4.22	4.12
33	4-ClC ₆ H ₄	Cyclopropyl	B	200-210 (0.3)		C ₂₂ H ₂₈ ClNO ₂	70.67	70.60	7.55	7.54	3.75	3.81
34	4-CH ₃ C ₆ H ₄	C ₆ H ₅ CH ₂ CH ₂	C ⁱ	<i>n</i>		C ₂₈ H ₃₅ NO ₂	80.54	80.75	8.45	8.40	3.35	3.14
35	2-Pyridyl	CH ₃	B	167-191 (1.3)		C ₁₉ H ₂₆ N ₂ O ₂	72.58	72.27	8.33	8.61	8.92	8.82
36	3-Pyridyl	CH ₃	B	<i>n</i>		C ₁₉ H ₂₆ N ₂ O ₂	72.58	72.62	8.33	8.61	8.92	8.97
37	4-Pyridyl	CH ₃	B	200-215 (1.6)		C ₁₉ H ₂₆ N ₂ O ₂	72.58	72.80	8.33	8.46	8.92	8.99
38	2-Pyridylmethyl	4-CH ₃ C ₆ H ₄	D	<i>n</i>		C ₂₆ H ₃₂ N ₂ O ₂	77.19	77.42	7.97	8.24	6.93	7.01
39	3-Pyridylmethyl	4-CH ₃ C ₆ H ₄	D	<i>n</i>		C ₂₆ H ₃₂ N ₂ O ₂	77.19	77.49	7.97	7.61	6.93	7.08
40	5-Methyl-2-pyrazinylmethyl	4-CH ₃ C ₆ H ₄	D		82-83.5	C ₂₆ H ₃₃ N ₃ O ₂	74.44	74.68	7.92	8.14	10.01	9.95
41	6-Methyl-2-pyrazinylmethyl	4-CH ₃ C ₆ H ₄	D	<i>n</i>		C ₂₆ H ₃₃ N ₃ O ₂	74.44	74.19	7.92	7.82	10.01	9.83
42	1-Phenyl-1-(2-pyrryl)-2,2,2-trifluoroethanol		<i>o</i>	94-97 (0.3)	73-75	C ₁₂ H ₁₀ F ₃ NO	59.75	59.84	4.18	4.29	5.81	5.56
43	9,10-Dihydro-9-(3-pyridyl)-9-anthrol		<i>o</i>		185-187	C ₁₉ H ₁₅ NO	83.49	83.62	5.53	5.76	5.13	5.17
44	9-(3-Pyridyl)-9-xanthenol		<i>p</i>		189-190	C ₁₈ H ₁₃ NO ₂	78.53	78.27	4.76	5.15	5.09	5.45
	 R ¹											
45	4-FC ₆ H ₄		B	200-203 (0.8)		C ₂₂ H ₂₈ FNO ₂	73.94	73.52	7.89	7.86	3.91	3.82
46	4-ClC ₆ H ₄		B	225-231 (1.3)		C ₂₂ H ₂₈ ClNO ₂	70.66	70.65	7.55	7.41	3.75	3.89
47	4-BrC ₆ H ₄		B	224-230 (1.0)		C ₂₂ H ₂₈ BrNO ₂	63.16	63.11	6.69	6.85	3.34	3.25
48	4-(CH ₃) ₃ C-C ₆ H ₄		B	231-234 (1.3)		C ₂₆ H ₃₇ NO ₂	78.94	78.83	9.43	9.69	8.09	8.26
49	2-Thienyl		B	203 (0.6)		C ₂₀ H ₂₇ NO ₂ S	69.53	69.50	7.88	8.12	4.05	3.91
	 R ¹											
50	5-Methyl-1-phenyl-4-pyrazolyl		B	229-230 (0.3)		C ₂₄ H ₃₁ N ₃ O ₂	76.76	76.85	7.79	7.93	11.20	11.40
51	C ₆ H ₅		B		154-156 ^e	C ₂₀ H ₂₅ NO · HCl	72.37	72.35	7.89	8.17	4.22	4.58
52	3-CF ₃ C ₆ H ₄		B	164-170 (1.0)		C ₂₁ H ₂₄ F ₃ NO	69.40	69.23	6.66	6.87	3.86	3.91
53	3,4,5-(CH ₃ O) ₃ C ₆ H ₂		B	222-226 (0.5)		C ₂₃ H ₃₁ NO ₄	71.66	71.66	8.11	8.19	3.63	3.54
54	4-C ₆ H ₅ C ₆ H ₄		B		192-193 ^e	C ₂₆ H ₂₉ NO · HCl	76.53	76.32	7.41	7.37	3.43	3.40
55	3-[4-(2-Diethylaminoethoxy)phenyl]indene		B	218-240 (4.5)		C ₂₁ H ₂₅ NO	82.05	81.90	8.20	8.34	4.55	4.53
56	4-[4-(2-Diethylaminoethoxy)phenyl]-1,2-dihydronaphthalene		B	210-213 (1.1)		C ₂₂ H ₂₇ NO	82.22	81.94	8.46	8.35	4.35	4.22
57	1-(4-Chlorobenzal)indane		A	190 (0.4)	63-65	C ₁₆ H ₁₃ Cl	79.83	79.78	5.44	5.66		
58	9-(4-Chlorobenzal)-9,10-dihydro-10-methylacridine		A		124-126 ^m	C ₂₁ H ₁₆ ClN	79.36	79.50	5.07	5.37	4.41	4.44

^a The intermediate aldehyde was prepared as described by J. Bernstein, H. L. Yale, K. Losee, M. Holsing, J. Martins, and W. A. Lott, *J. Am. Chem. Soc.*, **73**, 906 (1951). ^b The intermediate ketone has been described by K. Kratzl and E. Meisert, *Monatsh. Chem.*, **88**, 1056 (1957). ^c The intermediate ketone has been described by R. I. Meltzer and A. D. Lewis, *J. Org. Chem.*, **22**, 612 (1957). ^d The compound is 1-(4-chlorophenyl)-2-[4-(2-diethylaminoethoxy)-1-naphthyl]-2-propanol. ^e Melting point is for the hydrochloride. ^f The intermediate ketone was prepared by the procedure of C. D. Hurd and C. N. Webb, "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 217. ^g Recrystallized from acetone. ^h Recrystallized from methanol-Skellysolve B. ⁱ Recrystallized from benzene-Skellysolve C. ^j Recrystallized from isobutyl alcohol. ^k The required ketone was prepared from acenaphthene and benzoyl chloride in nitrobenzene at 0° in the presence of anhydrous aluminum chloride. The product melted at 98-99°. L. F. Fieser and E. B. Hershberg [*J. Am. Chem. Soc.*, **61**, 1278 (1939)] reported m.p. 98.5-99.5° and 101°. ^l The Grignard reaction was carried out in tetrahydrofuran. ^m Recrystallized from Skellysolve B. ⁿ Compound was not purified. ^o See Experimental section for method of preparation. ^p Prepared from 3-pyridyllithium and xanthenone in the same manner as described for **43**. Recrystallized from benzene.

TABLE II

KETONES^a

Compd.	R ¹	R ²	R ³	B.p., °C. (mm.)	Formula	% C		% H	
						Calcd.	Found	Calcd.	Found
1	CH ₃	H	4-(CH ₃) ₂ NCH ₂ CH ₂ O ^b	143 (0.65)	C ₁₂ H ₁₇ NO ₂	69.54	69.76	8.27	8.39
2	CH ₃	H	2-(CH ₃) ₂ NCH ₂ CH(CH ₃)O	130 (3.5)	C ₁₃ H ₁₉ NO ₂	70.56	70.63	8.65	8.52
3	CH ₃	H	3-(CH ₃) ₂ NCH ₂ CH(CH ₃)O	130 (0.5)	C ₁₃ H ₁₉ NO ₂	70.56	70.64	8.65	8.80
4	CH ₃	H	4-(CH ₃) ₂ NCH ₂ CH(CH ₃)O	140-141 (1.7)	C ₁₄ H ₁₉ NO ₂	70.56	70.91	8.65	8.37
5	CH ₃	4-CH ₃	2-(CH ₃) ₂ NCH ₂ CH(CH ₃)O ^c	151-152 (1.3)	C ₁₄ H ₂₁ NO ₂	71.46	71.27	9.00	8.97
6	CH ₃	3-CH ₃	4-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O	169 (1.4)	C ₁₅ H ₂₃ NO ₂	72.25	72.67	9.30	9.47
7	CH ₃	2,5-(CH ₃) ₂	4-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O ^d	162 (1.0)	C ₁₆ H ₂₅ NO ₂	72.96	72.81	9.57	9.67
8	CH ₃	3,5-(CH ₃) ₂	4-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O ^e	170-173 (1.7)	C ₁₆ H ₂₅ NO ₂	72.96	73.10	9.57	9.53
9	C ₂ H ₅	H	3-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O	165 (0.25)	C ₁₅ H ₂₃ NO ₂	72.25	72.29	9.30	9.13
10	n-C ₃ H ₇	H	4-(CH ₃) ₂ NCH ₂ CH(CH ₃)O	160-164 (0.8)	C ₁₅ H ₂₃ NO ₂	72.25	72.15	9.30	9.44
11	f, g			204 (1.0)	C ₁₅ H ₂₃ NO ₂	75.76	75.61	8.12	8.26
12	C ₆ H ₅	H	4-(C ₂ H ₅) ₂ NCOCH ₂ O	210-225 (0.2-1.2)	C ₁₉ H ₂₁ NO ₃	73.29	73.58	6.80	6.58
13	C ₆ H ₅	3-CH ₃	4-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O	210 (2.1)	C ₂₀ H ₂₅ NO ₂	77.13	77.03	8.09	7.89
14	C ₆ H ₅	3-Cl	4-(CH ₃) ₂ NCH ₂ CH(CH ₃)O ^h	220 (1.2)	C ₁₈ H ₂₀ ClNO ₂	68.02	67.95	6.34	6.95
15	CF ₃	H	4-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O	130-135 (1.5)	C ₁₄ H ₁₈ F ₃ NO ₂	58.12	57.84	6.27	6.19
16	C ₆ H ₅	H	4-[(C ₂ H ₅) ₂ NCH ₂] ₂ CHO	211-217 (0.6)	C ₂₄ H ₃₄ N ₂ O ₂	75.35	75.15	8.96	9.02
17	C ₆ H ₅	4-CH ₃ O	2-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O	217-220 (2.0)	C ₂₆ H ₂₈ NO ₃	73.36	73.00	7.70	7.55
18	C ₆ H ₅	4-CH ₂ =CHCH ₂ O	2-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O	188-198 (0.3)	C ₂₂ H ₂₇ NO ₃	74.75	74.78	7.70	7.45
19	C ₆ H ₅	4-n-C ₁₂ H ₂₅ O	2-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O	253-259 (0.7)	C ₃₆ H ₄₇ NO ₃	77.29	76.81	9.84	9.88
20	C ₆ H ₅	H	4-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O ⁱ	193-197 (0.3)	C ₁₉ H ₂₃ NO ₂	76.73	76.84	7.80	7.86
21	4-CH ₃ C ₆ H ₄	H	4-(C ₂ H ₅) ₂ NCH ₂ CH ₂ O ^j	190-205 (0.3)	C ₂₀ H ₂₅ NO ₂	77.13	77.02	8.09	8.02

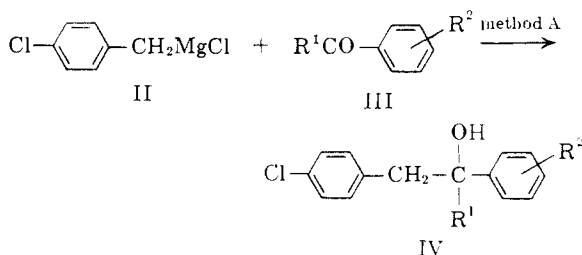
^a The hydroxy ketones required for the preparation of the ketones in this table were obtained from commercial sources (Aldrich Chemical Co., Inc., The Dow Chemical Co., or Tennessee Eastman Co.), were prepared as described in the literature, or are described in the Experimental section. ^b This compound has been reported by G. Di Paco and C. S. Tauro, *Ann. chim. (Rome)*, **48**, 1215 (1958).

^c The required hydroxy ketone was prepared by the Fries reaction as described by R. Baltzly, W. S. Ide, and A. P. Phillips, *J. Am. Chem. Soc.*, **77**, 2522 (1955).

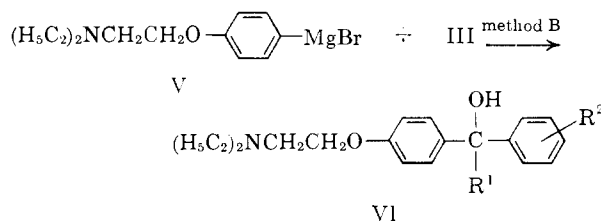
^d The required hydroxy ketone was prepared by the Fries reaction as described by K. v. Anwers, H. Bundesmann, and F. Wieners, *Ann.*, **447**, 162 (1926).

^e The required hydroxy ketone was prepared by the Fries reaction as described by F. Benington, R. D. Morin, L. C. Clark, Jr., and R. P. Fox, *J. Org. Chem.*, **23**, 1979 (1958).

^f The compound is 4-(2-diethylaminoethoxy)-1-acetonaphthone. ^g The required hydroxy ketone was prepared by the Fries reaction as described by H. Lederer, *J. prakt. Chem.*, **135**, 49 (1932). ^h The required hydroxy ketone was prepared by refluxing 4-hydroxybenzophenone and sulfuryl chloride in benzene for 4 hr. to give a product melting at 178-180°. M. Nencki and E. Stoerber [*Ber.*, **30**, 1772 (1897)] reported m.p. 176°. ⁱ Preparation of this compound is described in U. S. Patent 2,914,562 (R. E. Allen, F. P. Palopoli, E. L. Schumann, and M. G. Van Campen, Jr., to the Wm. S. Merrell Co., Nov. 24, 1959).

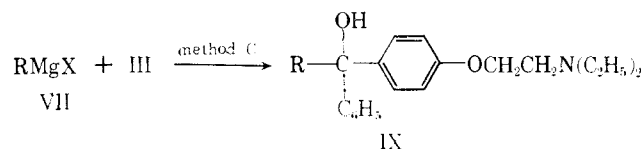


Method A involves the reaction of *p*-chlorobenzylmagnesium chloride (II) with a ketone (III), generally a derivative of acetophenone or benzophenone, in which the dialkylaminoalkoxy group is part of the ketone moiety. The Grignard reagent used in method B is 4-

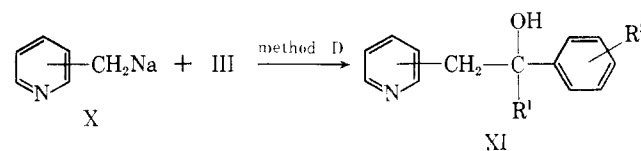


(2-diethylaminoethoxy)phenylmagnesium bromide (V). The ketone III did not necessarily carry a basic substituent. In some cases, the carbinols spontaneously lost water during the work-up yielding the correspond-

ing ethylene derivative. Attempts to prepare V in ether were uniformly unsuccessful, but V was formed smoothly and in good yield when tetrahydrofuran was used as the solvent. Preparation of the Grignard reagent in this manner was discovered independently by Lednicer and co-workers.⁸ Another advantage of tetrahydrofuran as a solvent for Grignard reactions is the increased solubility of the Grignard complexes in this solvent as compared with that of ether.



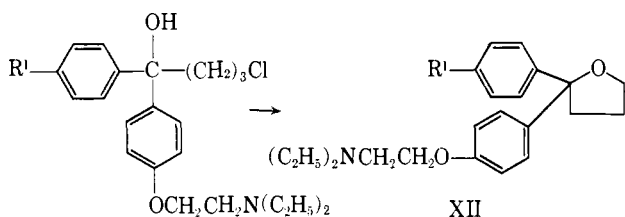
The reaction of various Grignard reagents (VII) with 4-(2-diethylaminoethoxy)benzophenone [III, R¹ = phenyl; R² = 4-OCH₂CH₂N(C₂H₅)₂] comprises method C. Method D involves the reaction of the



(8) D. Lednicer, J. C. Babcock, S. C. Jyster, J. C. Stucki, and G. W. Duncan, *Chem. Ind. (London)*, 2098 (1961).

sodio derivative of a methylpyridine (X), or a methylpyrazine, with 4-methylbenzophenone (III, $R^1 = C_6H_5$; $R^2 = 4-CH_3$), to give the corresponding carbinol XI. This method was not restricted to 2- and 4-picolines, but was also successful using 3-picoline. Formation of sodium salts of 2- and 4-picolines has been long known, but it was not until 1951 that Brown and Murphey⁹ observed such a reaction with 3-picoline. We have, however, found, as would be expected, that the latter reacts less readily with sodamide than does its isomers. Both 2- and 4-picoline react with sodamide to form the respective sodium salts at room temperature with evolution of heat. The formation of the sodium salt of 3-picoline does not occur at room temperature, but it is necessary to heat the reactants on the steam bath for 1 hr. This difference in reactivity allows one to form a monosodium salt from 3,4-lutidine.¹⁰

Several γ -chlorobutyrophenones were allowed to react with 4-(2-diethylaminoethoxy)phenylmagnesium bromide. The products isolated were not the γ -chlorobutylcarbinols. The carbinols spontaneously lost HCl, and the substances actually isolated are pre-



sumed to be 1,1-disubstituted tetrahydrofurans (XII).

The various ketones required for preparation of the carbinols and other compounds in Table I, which have not been described previously in the literature, are described in Table II. Known ketones were obtained from commercial sources, or were prepared by procedures in the literature.

Pharmacology.—Two methods were used for the determination of plasma cholesterol in the experiments reported here: (1) the method of Zak,¹¹ and (2) a modification of Abell's method.¹² Both methods measure cholesterol and at least part of the desmosterol if it is present.^{4,6b,13} Therefore "plasma cholesterol" as determined in these studies actually represents cholesterol plus part or all of any desmosterol present. No separate colorimetric determinations of desmosterol were done. Therefore a detailed comparison of activities of different drugs can be made only when the same cholesterol method was used in evaluating the drugs.

A. Routine Screening for Hypocholesteremic Activity.—The hypocholesteremic activity of the compounds in Table I was determined in mice by the method previously described⁷ using the method of Zak¹¹ for the cholesterol determinations. The active compounds are listed in Table III. Because of the

(9) H. C. Brown and W. A. Murphey, *J. Am. Chem. Soc.*, **73**, 3308 (1951).

(10) Two products from the monosodium salt of 3,4-lutidine were described in our previous paper⁷ (Table I, **10** and **11**). It is necessary to point out that **11** is 1,1-diphenyl-2-(3-methyl-4-pyridyl)ethanol, and not 1,1-diphenyl-2-(2-methyl-4-pyridyl)ethanol as indicated erroneously in the table.

(11) B. Zak, R. C. Dickenman, E. G. White, H. Burnett, and P. J. Chorney, *Am. J. Clin. Pathol.*, **24**, 1307 (1954).

(12) G. F. Lambert, J. P. Miller, R. T. Olsen, and D. V. Frost, *Proc. Soc. Exptl. Biol. Med.*, **97**, 544 (1958).

(13) I. D. Frantz, Jr., M. L. Moberley, and G. J. Schroetter, Jr., *Progr. Cardiovascular Diseases*, **2**, 511 (1960).

TABLE III
RESULTS OF ROUTINE SCREENING FOR HYPOCHOLESTEREMIC
ACTIVITY IN MICE

Compd. ^a	Daily dose, mg./kg.	Response, % reduction ^b
2	300	29
	100	20
3	125	47
	10	15
4	220	26
	10	3
6	375	29
7	312	25
	100	16
8	175	26
10	300	28
	10	0
12	100	45
	10	22
13	175	43
14	100	40
	10	c
21	100	43
	10	3
22	100	22
23	100	67
	100	50
	10	d
24	100	42
	10	20
25	156	37
	10	4
28	100	39
	10	40
	5	20
	1	16
29	100	65
	10	55
	5	50
	1	39
30	100	46
	10	43
	5	30
	1	18
31	312	49
32	100	28
33	25	33
34	100	31
40	188	34
46	38	26
Triparanol	100	49
	10	27
	5	25
	1	18

^a The numbers refer to the compounds in Table I. ^b % reduction = $100 \left(1 - \frac{\text{mg./100 of cholesterol, treated mice}}{\text{mg./100 of cholesterol, control average}} \right)$.
^c 8% increase. ^d 10% increase.

normal variability of cholesterol levels in mice, a decrease of less than 20% is not considered significant and only compounds causing a decrease greater than 20% at some dose are included. Toxicity permitting, all compounds were tested at a dose of 100 mg./kg. or higher.

The first 24 compounds are, for the most part, quite closely related to triparanol. Of these, only two (12 and 24) showed activity at all comparable to that of triparanol.

The next series of compounds (25–31) are triaryl-methanol derivatives. Three very active compounds

TABLE IV
EFFECT OF TRIPARANOL AND COMPOUND 29 ON PLASMA CHOLESTEROL IN THE MOUSE

Compl.	Daily dose, mg./kg.	Wt. gain, g./6 mice	Plasma cholesterol, mg./100 \pm S.E.M.	Significance (compared to control) (analysis of variance)
Control	...	+14	200 \pm 14.6	...
29	5	+17	199 \pm 6.8	$p < 0.01$
29	1	+21	122 \pm 6.8	$p < 0.01$
Triparanol	5	+5	149 \pm 11.5	$0.01 < p < 0.05$
Triparanol	1	+24	164 \pm 9.2	$0.01 < p < 0.05$

TABLE V
EFFECT OF TRIPARANOL AND COMPOUND 29 ON PLASMA CHOLESTEROL IN THE RAT

Group	Compl.	Daily dose, mg./kg. ^a	Number of rats	Plasma cholesterol, mg./100 \pm S.E.M.	Significance (compared to control) (analysis of variance)
1	Control	...	6	66.5 \pm 1.8	...
2	29	0.1	5	56.0 \pm 1.6	$0.01 < p < 0.05$
3	29	0.3	5	62.8 \pm 2.9	$0.05 < p$
4	29	1.0	5	64.8 \pm 3.3	$0.05 < p$
5	29	3.0	6	51.7 \pm 2.4	$p < 0.01$
6	Control	...	5	76.0	...
7	Triparanol	10.0	5	52.5	...

^a Administered subcutaneously in corn oil.

were found in this group. Two compounds, **28** and **30**, were found to have activity comparable to that of triparanol, while **29** was found to be significantly more active than triparanol. Indeed, **29** is the only compound we have found which will cause a significant reduction in the plasma cholesterol level of mice at a dose of 1 mg./kg. administered by the oral route. Of the remaining carbinols (**32-44**), only **33** had activity comparable to triparanol. Five of the tetrahydrofuran derivatives were prepared (**45-49**), and the only one to show significant activity was **46**. The ethylene derivatives (**50-58**) were all inactive.

B. Comparison of Hypocholesteremic Activity of Triparanol and α -[4-(2-Diethylaminoethoxy)phenyl]- α -phenyl-5-acenaphthenemethanol (Table I, 29) in the Mouse.—Male mice weighing about 30 g. were housed in groups of six and weighed as a group at the beginning and at the end of the treatment period of 2 weeks. Drugs were mixed with the diet (ground mouse breeder chow), which was fed *ad lib.* At the end of the feeding period, the mice were bled by cardiac puncture, and plasma cholesterol concentrations were determined by the method of Zak.¹¹ These results are summarized in Table IV.

It can be seen that compound **29** and triparanol lowered the plasma cholesterol level, with the former being more effective at both dose levels.

C. Hypocholesteremic Activity of Triparanol and α -[4-(2-Diethylaminoethoxy)phenyl]- α -phenyl-5-acenaphthenemethanol in the Rat.—The compounds were dissolved in corn oil and injected subcutaneously in rats once daily for 7 days. The control animals were injected with equivalent volumes of corn oil. At the end of the experiments, the animals were bled by cardiac puncture and plasma cholesterol levels were determined. The results are summarized in Table V. The two drugs were given in different experiments on separate occasions, and the cholesterol determinations were done by different methods. Data for the dose-response curve for **29** and the appropriate control were obtained by Abell's method,¹² using a plasma sample from each rat. According to Hollander^{6b} and Frantz,¹³ the Abell

method measures about 50-60% of the desmosterol present as well as the cholesterol. The "plasma cholesterol" data in Table V (expt. 2-5), therefore, are higher than the actual cholesterol concentration, but lower than the actual cholesterol plus desmosterol concentration.

The data for the rats given triparanol and the corresponding control, which are included for comparison, were obtained by the method of Zak,¹¹ using plasma which had been pooled after removing the cells by centrifugation. Zak's procedure for determining cholesterol is reported to measure desmosterol equally with cholesterol.^{4,13} The "plasma cholesterol" concentration recorded for triparanol in Table V (expt. 7), therefore, probably closely approximates the actual cholesterol plus desmosterol concentration.

Compound **29** lowered plasma cholesterol at dose levels of 0.1 and 3.0 mg./kg./day, but dose levels intermediate were ineffective. The reason for this is unknown. The data on triparanol also give an indication of an effect, but since pooled plasma was used, no statistics can be calculated. Clearly, as pointed out above, the results of expt. 2-5 are not directly comparable with the results of expt. 7, but the data do confirm that both drugs are effective agents for lowering the plasma cholesterol levels of rats.

D. Effect of Triparanol and α -[4-(2-Diethylaminoethoxy)phenyl]- α -phenyl-5-acenaphthenemethanol on Total Sterol Levels in the Rat.—Using pooled plasma from groups 1 and 5 in one experiment, and from 6 and 7 (Table V) in another experiment, chloroform extracts of the nonsaponifiable plasma lipids were prepared by saponifying 1 vol. of plasma with 12.5 vol. of alcoholic potassium hydroxide at 70° for 60 min. The alkaline solution was made by diluting 12 ml. of a 33% w/w. KOH solution to 100 ml. with absolute redistilled alcohol. After saponification, an equal volume of water was added; the mixture was cooled and extracted three times with 25 ml. of petroleum ether (Skellysolve B). The combined petroleum ether extracts were evaporated at 60° under nitrogen and the residue was redissolved in 1 ml. of chloroform. The

chloroform solutions were then investigated by gas chromatography, again on two different occasions, using somewhat different conditions as noted below.

A mixture of desmosterol and cholesterol was used to calibrate the instrument¹⁴ in order to obtain the total sterol data for samples 1 and 5. Comparison of curves from sample 1 (control) with the calibration curves gave a value of 5.5 mg. of total sterol/ml. of chloroform extract. No peak corresponding to desmosterol, only a single peak corresponding to cholesterol, was observed. The total sterol concentration of sample 5 (29) was 1.7 mg./ml., and a peak corresponding to desmosterol was observed, in addition to the cholesterol peak. Comparison of the two peaks indicate that 75% of the total sterol concentration was due to desmosterol.

Similar data for triparanol were obtained with a different column¹⁵ but calibration curves were not obtained. Comparison of the areas under the peak from sample 6 (control) with that from sample 7 (triparanol) indicate clearly that a substantial reduction in total plasma sterol has occurred in the animals treated with triparanol. No peak corresponding to desmosterol was observed with sample 6, but two peaks were observed with sample 7, and the desmosterol peak represented 55% of the total sterol content of the sample.

E. Effect of Triparanol and α -[4-(2-Diethylaminoethoxy)phenyl]- α -phenyl-5-acenaphthenemethanol on Reproduction in the Rat.—Wexler¹⁶ has reported that "triparanol-treated rats showed marked interference with their normal reproductive activity, *i.e.*, prolonged gestation, increased number of stillborn, and resorption of fetuses." Therefore, we compared the effect of compound 29 and triparanol on reproduction in the rat.

Twenty-four virgin female Badger rats, 92 days old, and 12 adult males were housed together in 6 cages, 4 females and 2 males per cage. After 1 week administration of the drugs was started. Two cages of rats were kept as controls, two cages received triparanol, and two cages received compound 29. The drugs were mixed with the ground Purina laboratory chow, so that the daily oral intake of each drug was approximately 25 mg./kg. The females and their offspring were observed for a period of 6 weeks after mating. The administration of the drugs was continued during this period.

The 8 females not receiving either drug all produced litters, and the average litter size was 11. Only two females receiving triparanol produced litters and the average size was 6. There were no live births. Five females treated with 29 had litters. The average size was 8 with no live births. The stillborn from the treated females showed gross developmental abnormalities.

These effects mitigated against submitting compound 29 for clinical trial, even though, as far as potency is concerned, it satisfies the requirement of being effective at a substantially lower dose than is triparanol.

(14) Stationary phase, 2% XE-60; column temperature, 215°; carrier, argon, 1.4 kg./cm.²; volume of injectate, 0.002 ml. for sample 1, and 0.01 ml. for sample 5.

(15) Stationary phase, 0.7% Pluronic F-68; column temperature, 222°; carrier, argon, 1.4 kg./cm.²; volume of injectate, 0.003 ml. for sample 6, and 0.01 ml. for sample 7.

(16) B. C. Wexler, *Endocrinology*, **74**, 64 (1964).

Experimental¹⁷

***p*-Bromophenyl 2-Diethylaminoethyl Ether.**—Sodium (25.3 g., 1.1 g.-atoms) was dissolved in 250 ml. of dry ethanol followed by addition of 119 g. (1.0 mole) of 4-bromophenol in 100 ml. of ethanol. The mixture was stirred and refluxed for 1 hr. Following addition of 149 g. (1.1 moles) of 2-diethylaminoethyl chloride, refluxing was continued overnight. The reaction mixture was cooled and filtered, and the filtrate was taken to dryness. The residue was treated with ether or chloroform and extracted with dilute NaOH and then with water. The organic layer was dried and then stripped, and the residue was subjected to vacuum distillation twice through a 20-cm. packed column, to yield 216 g. (79.4%) of colorless oil, b.p. 115–124° (1.0 mm.), n_D^{20} 1.5291.

Anal. Calcd. for C₁₂H₁₈BrNO: C, 52.95; H, 6.67; N, 5.15. Found: C, 53.09; H, 6.69; N, 5.22.

4'-Hydroxy-2,2,2-trifluoroacetophenone.—4'-Methoxy-2,2,2-trifluoroacetophenone¹⁸ was prepared from 4-methoxyphenylmagnesium bromide and lithium trifluoroacetate by the procedure of Rausch, *et al.*¹⁹ Freshly fused pyridine hydrochloride, 100 g., and 33 g. (0.16 mole) of the methoxy ketone were stirred and heated at 235° for 1 hr. The reaction mixture was dissolved in dilute HCl, and the product was taken up in ether. The ether was removed and the residue was crystallized from benzene to give 23 g. (75%) of product, melting at 114°.

Anal. Calcd. for C₈H₅F₃O₂: C, 50.53; H, 2.65. Found: C, 50.63; H, 2.44.

1-Phenyl-1-(2-pyrrolyl)-2,2,2-trifluoroethanol.—The Grignard reagent from 8 g. (0.33 g.-atom) of magnesium and 36 g. (0.33 mole) of ethyl bromide in 250 ml. of dry ether was cooled to -15° and maintained under a nitrogen atmosphere. A solution of 22 g. (0.33 mole) of pyrrole in 25 ml. of ether was added at such a rate that the temperature remained at -15°, and a solution of 58 g. (0.34 mole) of 2,2,2-trifluoroacetophenone (Matheson Coleman and Bell) in 50 ml. of ether was added. Hydrolysis was accomplished with ice-cold ammonium chloride solution. The product was taken up in ether, dried, and distilled. The distillate solidified and was crystallized from cyclohexane (Table I, 42).

9,10-Dihydro-9-(3-pyridyl)-9-anthrol.—3-Pyridyllithium (0.23 mole) was prepared according to the procedure of Gilman and Spatz.²⁰ The ether solution was kept under nitrogen and cooled to -60°. Anthrone (38.8 g., 0.2 mole) was added in small portions, and the reaction mixture was allowed to warm to room temperature before it was poured onto ice. The solid was collected, washed with ether, and crystallized from ethanol (Table I, 43).

Preparation of the Ketones in Table II.—The sodium salt of the hydroxy ketone was allowed to react with the appropriate dialkylaminoalkyl chloride in the manner described above for the preparation of *p*-bromophenyl 2-diethylaminoethyl ether.

Preparation of Carbinols and Related Compounds. Method A.—The ketone and *p*-chlorobenzylmagnesium chloride were allowed to react in the manner previously described.⁷

Method B.—A solution of 27 g. (0.1 mole) of *p*-bromophenyl 2-diethylaminoethyl ether in 100 ml. of dry tetrahydrofuran and 2.4 g. (0.1 g.-atom) of magnesium turnings were stirred and heated under reflux until the reaction started. The source of heat was removed until the exothermic reaction ceased, and then refluxing was continued for 2 hr. A solution of the ketone (0.1–0.15 mole) in 50 ml. of tetrahydrofuran was added slowly, and then the solution was heated under reflux for 2 hr. The flask was cooled in an ice bath, and the Grignard complex was hydrolyzed by dropwise addition of 15 ml. of saturated ammonium chloride solution. The solid was collected on a filter, the filtrate was stripped, and the residue was subjected to vacuum distillation. The hydrolysis could also be effected by dropwise addition of 100 ml. of 20% ammonium chloride solution.

Method C.—The Grignard reagent was formed in ether. The reaction was worked up as described under B.

Method D.—The sodium salt of the appropriate picoline or methylpyrazine was prepared, and the reaction was carried out, as previously described.⁷ It was necessary to heat β -picoline and sodamide on the steam bath to obtain β -picolylsodium.

(17) All melting points are uncorrected. Most of these compounds were made prior to 1962, before the journals of the American Chemical Society announced the requirement of melting point corrections.

(18) R. Fuchs and G. J. Park, *J. Org. Chem.*, **22**, 993 (1952).

(19) D. A. Rausch, L. E. Coleman, Jr., and A. M. Lovelace, *J. Am. Chem. Soc.*, **79**, 4983 (1957).

(20) H. Gilman and S. M. Spatz, *ibid.*, **62**, 446 (1940).

Acknowledgment.—The microanalyses were provided by Mr. Elmer Shelberg, Mr. Orville Kolsto, and staff of the Abbott Microanalytical Laboratory. The

gas chromatographic analyses were carried out by Dr. Ilmar Merits and Mrs. Taimi Anderson.

The Synthesis of Phencyclidine and Other 1-Arylcyclohexylamines

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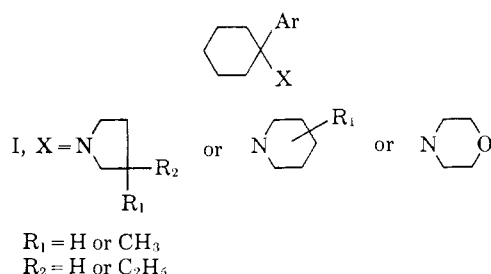
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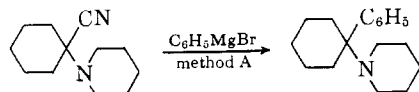
Various 1-arylcyclohexylamines were synthesized for evaluation as central nervous system depressants. The compounds were prepared by several procedures. 1-(1-Phenylcyclohexyl)piperidine, the first compound of this type synthesized, was prepared from 1-piperidinocyclohexanecarbonitrile by replacement 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-piperidinocyclohexanecarbonitrile¹ 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 phencyclidine³ 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-



amino-cyclohexanecarbonitrile by arylmagnesium halide (method A), as illustrated below for phencyclidine.



(1) A. Kotz and T. Merkel, *J. prakt. Chem.*, **113**, 49 (1926).

(2) G. Chen, *Federation Proc.*, **17**, 358 (1958).

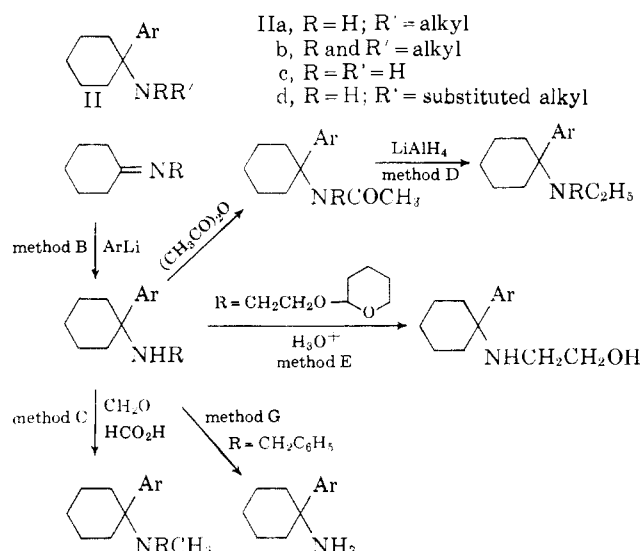
(3) Sernyl or Sernylan® is the Trade-mark for phencyclidine, 1-(phenylcyclohexyl)piperidine hydrochloride.

(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. Bajgel, *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. Sisondo, 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. Mundeeler, *Agressologie*, **1**, 511 (1960); (f) B. J. Muir, V. Evans, and J. J. Mulcahy, *Brit. J. Anaesthesia*, **33**, 51 (1961).

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 iminium 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 IIId were prepared by method B. For secondary amines of type IIId with a hydroxyl group in the side chain, a tetrahydropyranyl ether was used as a protecting group (method F). Thus, 2-cyanomethoxytetrahydropyran⁶ 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

(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).