under hydrogen at an initial pressure of 3.87 kg./cm.² (55.0 p.s.i.) on a Parr hydrogenator. A decrease in hydrogen pressure of 1.62 kg./cm.² was observed (calcd., 1.64). After removal of the catalyst, the ethanol was evaporated on a rotary evaporator. The residue, on vacuum distillation, yielded a fraction which boiled at 144–158° (0.2 mm.) and which hardened into a white solid on cooling (9.78 g., 63%). Redistillation afforded 7.48 g. (76% recovery) of material boiling at 144–150° (0.2 mm.); a sample boiling at 150° (0.2 mm.) was used for analysis: infrared spectrum ($CHCl_3$): 2.85 (sh), 2.95 (sh), 3.42, 6.32, 6.89, 6.95 (sh), 7.30, 7.41 (sh), 7.95, 8.92, 9.15, 9.52 μ.

The tetrahydrochloride salt was prepared in the usual manner in 74% yield, m.p. 298–305° dec. after recrystallization from aqueous ethanol.

When a warm solution of 320 mg. of free base (1.5 mmoles) in ethanol was added to a warm solution of 1.28 g. (5.6 mmoles) of picric acid in ethanol, a yellow crystalline picrate formed instantly (1.46 g., 92%). Several recrystallizations from water, with better than 90% recovery each time, gave a product decomposing at 227°. Analysis indicated the sample to be a tetrapicrate monohydrate. The sample was dried at 70° for 72 hr. *in vacuo*.

Anal. Calcd. for $C_{17}H_{28}N_4 \cdot 4C_6H_3N_3O_7 \cdot H_2O$: C, 36.53; H, 3.68; N, 19.47. Found: C, 36.51; H, 3.78; N, 19.54.

Acknowledgment.—The authors are indebted to Dr. George E. Foley for the determination of the biological activity of these compounds in mammalian cell culture systems, and to Dr. Charlotte L. Maddock and Dr. Sidney Farber for the biological data against transplantable rodent tumors. We also wish to express our appreciation to Mr. James H. Gunnerson for the infrared spectra and to Mrs. Ann M. Ronan and Mr. Charles A. Lundberg, Jr., for technical assistance during part of this investigation.

Compounds Derived from the Mannich Bases of β-Phenylpropiophenone

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Various substituted β-phenylpropiophenones, obtained by hydrogenating the appropriate chalcone, have been allowed to react with secondary bases and formaldehyde to give the Mannich bases II. These have been reduced or treated with Grignard reagents, the resulting alcohols have been acylated and dehydrated, and the olefinic products of dehydration have been hydrogenated to the paraffins. Cyclization of the chalcones provided a series of substituted indanones which were treated in the same manner as the β-phenylpropiophenones. Many of the compounds prepared had interesting pharmacological activities.

Whereas the use of the Mannich bases of alkylophenones[1] and desoxybenzoin[2] as valuable intermediates for the preparation of physiologically active compounds is of long standing, little work has been reported[3] on the Mannich bases of the β-phenylpropiophenones, either as chemical entities or potential pharmaceuticals.

Taking the substituted phenylpropiophenones (I) (Scheme I) we have prepared the Mannich bases (II) which with sodium borohydride gave the secondary alcohols (III, R_5 = H) or with a Grignard reagent gave the tertiary alcohols (III, R_5 = alkyl, cycloalkyl, phenyl, or aminoalkyl). The tertiary alcohols could then be dehydrated by boiling gently with HCl in acetic acid to give the olefins (IV) usually as a mixture of *cis-trans* isomers. With ethylmagnesium bromide as the Grignard reagent the resulting tertiary alcohol (III, $R_1 = R_2 = H$; $R_3 = R_4 = CH_3$; $R_5 = CH_3CH_2$) could theoretically dehydrate in both of two ways to give the olefin of type IV and, by eliminating a proton from the ethyl group, compound VI. In earlier work,[4] the somewhat simpler tertiary alcohol VII eliminated away from the ethyl group to give VIII analogous to type IV. However, our dehydrated material was shown to be VI by both the isolation of acetaldehyde as its 2,4-dinitrophenylhydrazone from the products of ozonolysis and the n.m.r. spectrum which showed two pairs of doublets (mixture of *cis-trans* isomers) at τ 3.9–4.2, indicative of a vinyl proton.

The catalytic reduction of these dehydrated compounds (IV) proceeded well only when R_5 was an alkyl group; when R_5 was phenyl, the alkane (V) was prepared directly from the substituted benzhydrol (III, $R_5 = C_6H_5$) by reduction with sodium in liquid ammonia.

The pyridyl chalcone IX obtained by condensing 2-acetopyridine with benzaldehyde[5] gave, on reduction, the analogous alkanone[6] which with phenyllithium gave the tertiary alcohol X; the same alcohol was obtained by reacting 2-pyridyllithium with β-phenylpropiophenone, though in neither reaction was the yield good. With hydrazine and sodium ethoxyethoxide[7] the pyridyl chalcone IX gave the pyridyl-

(1) (a) F. F. Blicke, *Org. Reactions*, **1**, 303 (1942); (b) A. L. Morrison and H. Rinderknecht, *J. Chem. Soc.*, 1510 (1950); (c) A. Pohland, H. R. Sullivan, and R. E. McMahon, *J. Am. Chem. Soc.*, **79**, 1442 (1957); (d) A. W. Ruddy and J. S. Buckley, Jr., *ibid.*, **72**, 718 (1950); (e) T. D. Perrine, *J. Org. Chem.*, **18**, 898 (1953); (f) I. I. Nazarov and E. M. Cherkasova, *J. Gen. Chem. USSR*, **25**, 2121 (1955); (g) A. Takada, *Chem. Pharm. Bull.* (Tokyo), **9**, 908 (1961); (h) Von Benno Reichert and A. Mayr, *Arzneimittel-Forsch.*, **13**, 991 (1963); (i) Von Benno and H. Partenheimer, *ibid.*, **13**, 1013 (1963); (j) J. J. Denton, V. A. Lawson, W. B. Neier, and R. J. Turner, *J. Am. Chem. Soc.*, **71**, 2050 (1949); (k) J. J. Denton, W. B. Neier, and V. A. Lawson, *ibid.*, **71**, 2053 (1949); (l) J. J. Denton, H. P. Schedl, W. B. Neier, and V. A. Lawson, *ibid.*, **71**, 2054 (1949).

(2) (a) J. J. Denton, R. J. Turner, W. B. Neier, V. A. Lawson, and H. P. Schedl, *ibid.*, **71**, 2048 (1949); (b) O. L. Madzhoyan and G. M. Pogosyan, *Izv. Akad. Nauk. Arm. SSR*, **13**, 357 (1960).

(3) Since the completion of the work here described, the preparation of the dimethylamino and the morpholino Mannich bases of the unsubstituted β-phenylpropiophenone has been described: A. Lespagnol, R. Hazard, C. Lespagnol, J. C. Cazin, and A. Renier-Cornec, *Congr. Sci. Pharm.*, 21e, Pisa, 1961, *Conf. Commun.*, p. 660; *Chem. Abstr.*, **59**, 6401 (1963). More recently, representative examples of the tertiary alcohols have been described: A. Lespagnol, C. Lespagnol, J. C. Cazin, and M. Cazin, *Bull. Soc. Chim. France*, 2747 (1963).

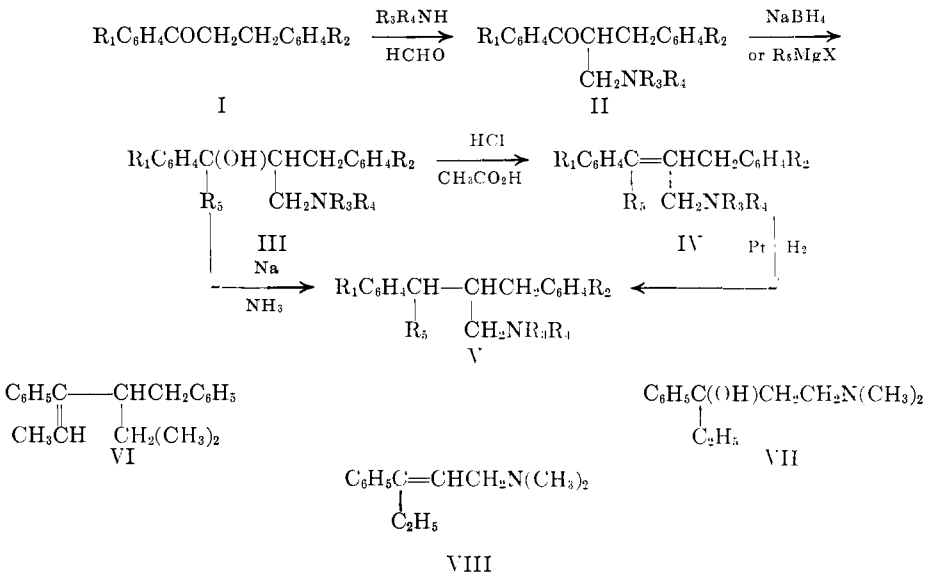
(4) J. H. Burckhalter and S. H. Johnson, *J. Am. Chem. Soc.*, **73**, 4827 (1951).

(5) C. S. Marvel, L. E. Coleman, and G. P. Scott, *J. Org. Chem.*, **20**, 1785 (1955).

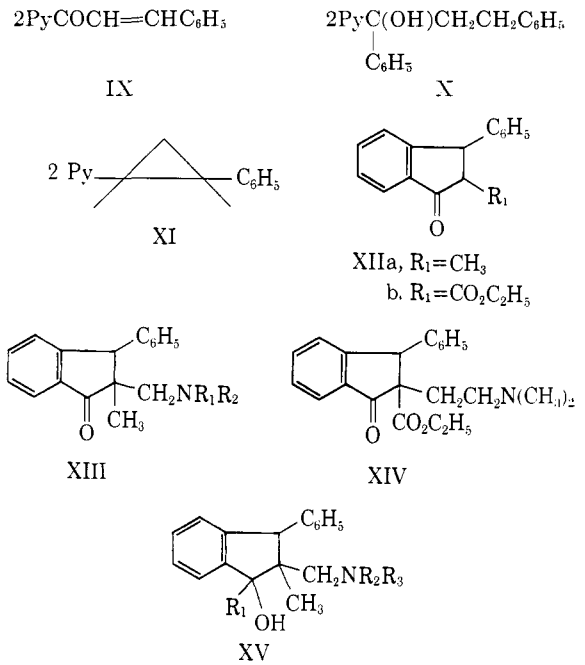
(6) A. Pinner, *Ber.*, **34**, 4234 (1901).

(7) G. Isardelli and O. Jeger, *Helv. Chim. Acta*, **32**, 1817 (1949).

SCHEME I



phenylcyclopropane XI in good yield. The cyclization of disubstituted acrylophenones with aluminum chloride to substituted indanones is well known.[8] We used 2-methyl-3-phenylindanone (XIIa) as a ketone in a Mannich reaction to get bases of structure XIII. The use of 2-ethoxycarbonyl-3-phenylindanone (XIIb) in a Mannich reaction gave no basic product, but it could be substituted at the active hydrogen



using sodium and diethylaminoethyl chloride to give the homolog of the Mannich base XIV. With Grignard reagents the tertiary alcohols XV were obtained which, in one case (XV, $R_1 = C_2H_5$; $R_2 = R_3 = CH_3$), gave the alkene on dehydration and the alkane on subsequent reduction.

In the case of one compound (III, $R_1 = R_2 = H$; $R_3 = R_4 = CH_3$; $R_5 = C_2H_5$) where toxicity problems were encountered, the N-oxide was prepared by reacting the base with monoperphthalic acid.

(8) C. F. Koelsch, *J. Org. Chem.*, **26**, 2590 (1961).

Experimental[9]

Chalcones.—The chalcones used in this work were known compounds and were prepared by the standard chalcone synthesis[10]; 2-cinnamoylpyridine required special conditions.[5]

β-Phenylpropiophenones.—These were prepared by hydrogenating the appropriate chalcones using standard techniques.[11] The only novel compound in the group was β-(*p*-methoxyphenyl)-*o*,*p*-dimethoxypropiophenone, m.p. 71–73°, prepared from the commercially available 4,2′,4′-trimethoxychalcone.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 72.0; H, 6.7. Found: C, 71.6; H, 6.8.

Mannich Reaction.—Although the general method used for this reaction was that described by Blicke,[12] we found that optimum yields were achieved when reflux was continued for 16 hr. in an oil bath maintained at 105°. Both too slow and too rapid a rate of reflux gave smaller yields, although the unreacted ketone could always be recovered. The physical constants and other data of the bases prepared are given in Table I.

3-Phenylindanones.—2-Ethoxycarbonyl-3-phenyl-1-indanone[8] and 2-methyl-3-phenyl-1-indanone[8] were prepared in good yield by the literature methods.

1,3-Diphenylpropanols. A. Secondary Alcohols.—The appropriate Mannich base (1 mole) in ethanol was treated at room temperature with an aqueous solution of potassium borohydride (1 mole), then left overnight when the solution was concentrated, and the required alcohol was isolated with ether and crystallized from ether-petroleum ether (b.p. 40–60°) mixtures.

B. Tertiary Alcohols.—These were prepared by adding the ethereal solution of the Mannich base to an ethereal Grignard solution and isolating the product by adding aqueous ammonium chloride[13]; the basic dimethylaminopropylmagnesium chloride was prepared following the conditions of Marxer.[14] The compounds obtained are listed in Table II.

Quaternaries.—These were made by refluxing the base with excess of alkyl halide in acetone for 2 hr. followed by crystallization either from acetone or from acetone–ether mixtures.

2-Dimethylaminomethyl-1,3-diphenyl-3-pentanol N-Oxide.—2-Dimethylaminomethyl-1,3-diphenyl-3-pentanol (III, $R_1 = R_2 = H$; $R_3 = R_4 = CH_3$; $R_5 = C_2H_5$) (1.8 g.) in chloroform (50 ml.) was treated at 15° with an ethereal solution of perphthalic acid (35 ml., 0.24 *M*, 1.4 moles) and allowed to stand at room temperature for 3 days then filtered and concentrated *in vacuo*

(9) Melting points are uncorrected, the work being completed before the announcement of the requirements for corrected melting points.

(10) E. P. Kohler and H. M. Chadwell, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 78.

(11) R. Adams, J. W. Kern, and R. L. Schriner, ref. 10, p. 101.

(12) F. F. Blicke, *Org. Reactions*, **1**, 303 (1942).

(13) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall Inc., New York, N. Y., 1954.

(14) A. Marxer, *Helv. Chim. Acta*, **24**, 209E (1941).

TABLE I

MANNICH BASES OF β-PHENYLPROPIOPHENONES

$R_1C_6H_4CH_2CHCOC_6H_3R_2$

$CH_2NR_3R_4$

Compd.	R_1	R_2	R_3	R_4	M.p., °C.	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1	H	H	CH_3	CH_3	67–68	79	$C_{18}H_{21}NO$	80.9	7.9	5.2	81.2	7.9	5.1
2	H	H	CH_3	CH_3	141[a]		$C_{18}H_{21}NO\cdot HCl$[b]	71.2	7.3	4.6	70.6	7.4	4.4
3	*p*-CH_3O	H	CH_3	CH_3	50–51	71	$C_{19}H_{23}NO_2$	76.7	7.8	4.7	76.9	7.8	4.6
4	*p*-CH_3O	H	CH_3	CH_3	98–100		$C_{19}H_{23}NO_2\cdot HCl$[b]	68.3	7.3	4.2	68.4	7.4	4.0
5	*p*-Cl	H	CH_3	CH_3	67–68	28	$C_{18}H_{20}ClNO$	71.6	6.3	4.7	71.4	6.3	4.7
6	H	*p*-CH_3O	CH_3	CH_3	170–171	78	$C_{19}H_{23}NO_2\cdot HCl$[b]	68.3	7.3	4.2	68.9	7.2	3.8
7	*m,p*-$(CH_3O)_2$	H	CH_3	CH_3	116–119	73	$C_{20}H_{25}NO_3\cdot HCl$[b]	66.0	7.2	3.8	65.9	7.1	3.7
8	*p*-CH_3O	*o,p*-$(CH_3O)_2$	CH_3	CH_3	136–138	69	$C_{21}H_{27}NO_4\cdot HCl$[b]	64.0	7.2	3.7	64.1	7.5	3.3
9	H	H	$(CH_2)_2O(CH_2)_2$		154–156[c]	84	$C_{20}H_{23}NO_2\cdot HCl$[b]	69.5	7.0	4.1	69.8	7.0	4.1

[a] Lit.[3] m.p. 145°. [b] Hydrochloride. [c] Lit.[3] m.p. 153–154°.

TABLE II

1,3-DIPHENYLPROPANOLS

R_5

$R_1C_6H_4CH_2CH—C—(OH)C_6H_4R_2$

$CH_2NR_3R_4$

Compd.	R_1	R_2	R_3	R_4	R_5	M.p., °C.	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
10	H	H	CH_3	CH_3	H	135–137	71	$C_{18}H_{23}NO$	80.3	8.6	5.2	79.9	8.6	4.7
11	H	H	CH_3	CH_3	H	225–226		$C_{18}H_{23}NO\cdot HCl$[a]	70.7	7.9	4.6	70.4	7.8	4.5
12	H	H	CH_3	CH_3	CH_3	115–117	85	$C_{19}H_{25}NO$	80.5	8.9	4.9	79.9	9.0	5.3
13	H	H	CH_3	CH_3	CH_3	208–209		$C_{19}H_{25}NO\cdot HCl$[a]	71.3	8.2	4.4	70.9	8.4	4.6
14	H	H	CH_3	CH_3	C_2H_5	122–124[a]	93	$C_{20}H_{27}NO$	80.8	9.2	4.7	80.9	9.3	4.7
15	H	H	CH_3	CH_3	C_2H_5	218–219[c]		$C_{20}H_{27}NO\cdot HCl$[a]	72.0	8.5	4.2	72.3	8.4	4.4
16	H	H	CH_3	CH_3	C_2H_5	176–178	75	$C_{20}H_{27}NO\cdot CH_3I$[d]	57.4	6.9	28.9[e]	57.7	6.6	28.4[e]
17	H	H	CH_3	CH_3	C_2H_5	133–136	50	$C_{20}H_{27}NO_2$[f]	76.6	8.7	4.5	76.2	8.8	4.3
18	H	H	CH_3	CH_3	C_2H_5	191–193		$C_{20}H_{27}NO_2\cdot HCl$[g]	68.7	8.1	4.0	68.2	8.1	3.9
19	H	H	CH_3	CH_3	*n*-C_3H_7	99–101	75	$C_{20}H_{29}NO$	81.0	9.4	4.5	81.0	9.4	4.1
20	H	H	CH_3	CH_3	*n*-C_3H_7	141–142		$C_{20}H_{29}NO\cdot HCl\cdot 0.5H_2O$[a]	70.6	8.8	3.9	71.2	8.3	4.2
21	H	H	CH_3	CH_3	*n*-C_5H_{11}	98–100	73	$C_{23}H_{33}NO$	81.4	9.8	4.1	81.0	9.8	4.2
22	H	H	CH_3	CH_3	*n*-C_5H_{11}	117–120		$C_{23}H_{33}NO\cdot HCl\cdot 0.5H_2O$[a]	71.9	9.2	3.6	71.5	8.8	3.8
23	H	H	CH_3	CH_3	C_6H_5	93–94[b]	81	$C_{24}H_{27}NO$	83.1	7.9	4.1	83.1	7.8	4.0
24	H	H	CH_3	CH_3	C_6H_5	207–208[i]		$C_{24}H_{27}NO\cdot HCl$[a]	75.5	7.4	3.7	75.3	7.7	3.8
25	H	H	CH_3	CH_3	C_6H_{11}	100–102	61	$C_{24}H_{33}NO$	82.0	9.5	4.0	82.2	9.6	4.2
26	H	H	CH_3	CH_3	C_6H_{11}	224–226		$C_{24}H_{33}NO\cdot HCl$[a]	74.1	8.8	3.6	74.2	8.8	3.9
27	H	H	CH_3	CH_3	$C_6H_5CH_2$	93–97	79	$C_{25}H_{29}NO$	83.1	8.6	3.9	83.2	8.4	4.1
28	H	H	CH_3	CH_3	$C_6H_5CH_2$	207–211		$C_{25}H_{29}NO\cdot HCl$[a]	75.6	8.1	3.6	75.5	7.6	3.8
29	H	H	CH_3	CH_3	$(CH_2)_3N(CH_3)_2$	80–82	98	$C_{28}H_{34}N_2O$	77.9	9.7	7.9	77.4	9.7	7.7
30	H	H	CH_3	CH_3	$(CH_2)_3N(CH_3)_2$	255–258		$C_{28}H_{34}N_2O\cdot 2HCl\cdot H_2O$	62.0	8.6	5.3	61.8	8.8	6.0
31	H	H	CH_3	CH_3	$(CH_2)_3N(CH_3)_2$	230–234	30	$C_{28}H_{34}N_2O\cdot 2CH_3Br$[k]	55.2	7.4	29.4[l]	54.7	7.6	29.2[l]
32	H	H	$(CH_2)_2O(CH_2)_2$		C_6H_5	200–201[m]	72	$C_{26}H_{29}NO_2HCl$[a]	73.6	7.1	3.3	74.0	6.9	3.5
33	H	*p*-CH_3O	CH_3	CH_3	C_6H_5	112–114	75	$C_{25}H_{29}NO_2$	80.0	7.8	3.7	79.7	7.2	4.2
34	H	*p*-CH_3O	CH_3	CH_3	C_6H_5	197–198		$C_{25}H_{29}NO_2\cdot HCl$[a]	72.9	7.3	3.4	72.7	7.7	3.8
35	H	*p*-Cl	CH_3	CH_3	C_6H_5	126–127	68	$C_{24}H_{26}ClNO$	75.9	6.9	3.7	76.3	7.0	4.0
36	H	*p*-Cl	CH_3	CH_3	C_6H_5	188–190		$C_{24}H_{26}Cl\cdot NO\cdot HCl$[a]	69.2	6.5	3.4	69.2	6.4	3.3
37	*p*-CH_3O	H	CH_3	CH_3	H	117–119	50	$C_{19}H_{23}NO_2$	76.2	8.4	4.7	76.2	8.5	4.3
38	*p*-CH_3O	H	CH_3	CH_3	H	177–179		$C_{19}H_{23}NO_2\cdot HCl$[a]	67.9	7.8	4.2	67.7	7.3	4.0
39	*p*-CH_3O	H	CH_3	CH_3	C_6H_5	93–95	89	$C_{25}H_{29}NO_2$	80.0	7.8	3.7	80.1	7.6	3.1
40	*p*-CH_3O	H	CH_3	CH_3	C_6H_5	130–135		$C_{25}H_{29}NO_2\cdot HCl\cdot 0.5H_2O$[a]	71.4	7.4	3.3	70.8	7.4	3.1
41	*p*-CH_3O	H	CH_3	CH_3	C_6H_5	218–219	90	$C_{25}H_{29}NO_2\cdot CH_3I$[d]	60.4	6.2	24.5[e]	60.8	6.2	24.7[e]
42	*p*-CH_3O	*p*-CH_3O	CH_3	CH_3	C_6H_5	149–150	35	$C_{26}H_{31}NO_3\cdot HCl$[a]	70.7	7.3	3.2	70.3	7.0	3.8
43	*m,p*-$(CH_3O)_2$	H	CH_3	CH_3	C_6H_5	184–185	62	$C_{26}H_{31}NO_3\cdot HCl\cdot 0.5H_2O$[a]	69.3	7.4	3.1	69.2	7.[illegible]	3.3
44	*p*-Cl	H	CH_3	CH_3	C_6H_5	119–121	87	$C_{24}H_{26}ClNO$	75.9	6.9	3.7	76.4	6.8	3.7
45	*p*-Cl	H	CH_3	CH_3	C_6H_5	116–119		$C_{24}H_{26}ClNO\cdot HCl\cdot H_2O$[a]	66.5	6.7	3.2	66.1	7.0	3.1

[a] Hydrochloride. [b] Lit.[3] m.p. 130°. [c] Lit.[3] m.p. 227°. [d] Methiodide. [e] Iodine analysis. [f] N-Oxide. [g] N-Oxide hydrochloride. [h] Lit.[3] m.p. 77–79°. [i] Lit.[3] m.p. 210°. [j] Dihydrochloride. [k] Methyl bromide diquaternary. [l] Bromine analysis. [m] Lit.[3] m.p. 210°.

to a white solid which was dissolved in chloroform and extracted exhaustively with dilute sodium carbonate solution. The chloroform solution was dried ($MgSO_4$), concentrated to low bulk, and then treated with petroleum ether (b.p. 40–60°) to turbidity. On standing, the required N-oxide was obtained as white needles, m.p. 134–137°, yield 0.85 g.

Anal. Calcd. for $C_{26}H_{27}NO_2$: C, 76.6; H, 8.7; N, 4.5. Found: C, 76.2; H, 8.8; N, 4.3.

On treating an ethereal solution of this compound with HCl a salt was obtained, m.p. 191–193°, $pK = 4.5$.

Anal. Calcd. for $C_{26}H_{27}NO_2\cdot HCl$: C, 68.7; H, 8.1; N, 4.0. Found: C, 68.5; H, 8.1; N, 3.9.

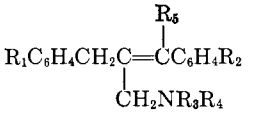
Dehydration of Tertiary Alcohols.—The method found most satisfactory for this dehydration was that described by Adamson.[15] The alcohol (0.01 mole) in glacial acetic acid (20 ml.) was refluxed with concentrated HCl (6 ml.) for 0.5 hr., then concentrated *in vacuo* to a solid and crystallized from 2-propanol. The compounds obtained are listed in Table III.

1-Dimethylaminomethyl-1,3-diphenylpentane.—The pentene hydrochloride (**50**) (2 g.) in ethanol (50 ml.) was shaken with platinic oxide (0.2 g.) in an atmosphere of hydrogen until 250 ml. was absorbed. The mixture was filtered, then concentrated to a glass and crystallized from ethanol–ether mixtures to give the required alkane, m.p. 137–140°, yield 1.1 g. Lack of absorption in the ultraviolet at 232 mμ showed the absence of any starting material.

(15) D. W. Adamson, *J. Chem. Soc.*, 144 (1949).

TABLE III

SUBSTITUTED STYRENES



Compd.	R_1	R_2	R_3	R_4	R_5	M.p., °C.	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
46	H	H	CH_3	CH_3	C_6H_5	202–204	90	$C_{24}H_{25}N\cdot HCl$	79.2	7.2	3.9	79.3	6.6	3.8
47	*p*-Cl	H	CH_3	CH_3	C_6H_5	193–196	84	$C_{24}H_{24}ClN\cdot HCl$	72.4	6.3	3.5	71.8	6.3	4.0
48	H	*p*-CH_3O	CH_3	CH_3	C_6H_5	167–174	84	$C_{25}H_{27}NO\cdot HCl$	76.2	7.2	3.6	76.6	7.4	3.5
49	H	H	$(CH_2)_2O(CH_2)_2$		C_6H_5	233–234	86	$C_{26}H_{27}NO\cdot HCl$	76.9	7.0	3.5	77.0	6.8	3.8
50[a]	H	H	CH_3	CH_3	C_2H_5[a]	100–110	78	$C_{20}H_{25}N\cdot HCl\cdot 0.5H_2O$	74.0	8.4	4.2	74.6	8.1	4.0
51[a,b]	H	H	CH_3	CH_3	C_2H_5[a,b]	143–145	79	$C_{21}H_{28}IN$	59.9	6.7	30.1[c]	59.7	6.9	30.7[c]

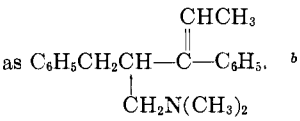
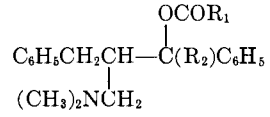
[a] This compound should be formulated as  [b] Quaternary methiodide of **50**. [c] Iodine analysis.

TABLE IV

ESTERS OF 1,3-DIPHENYLPROPANOLS



Compd.	R_1	R_2	M.p., °C.	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
52	C_2H_5	H	162–164	85	$C_{21}H_{27}NO_2\cdot HCl$[a]	69.7	7.8	3.9	69.8	7.6	3.8
53	C_2H_5	C_2H_5	180–182	90	$C_{23}H_{31}NO_2\cdot HCl$[a]	70.8	8.3	3.6	70.9	8.2	3.5
54	CH_3	C_2H_5	189–190	89	$C_{22}H_{29}NO_2\cdot HCl$[a]	70.3	8.1	3.7	70.2	7.7	3.5
55	CH_3	*n*-C_5H_{11}	178–180	88	$C_{25}H_{35}NO_2\cdot HCl$[a]	71.9	8.7	3.4	72.3	8.8	3.7

[a] Hydrochloride.

Anal. Calcd. for $C_{20}H_{27}N\cdot HCl$: C, 75.5; H, 8.9; N, 4.4. Found: C, 75.4; H, 8.8; N, 4.4.

2-Benzyl-N,N-dimethyl-3,3-diphenylpropylamine.—2-Dimethylaminomethyl-1,1,3-triphenylpropanol (**23**) (9 g.) in ethanol (50 ml.) was added to liquid ammonia (250 ml.), and the stirred suspension was treated at −50° with sodium (3.2 g.) in portions over 1 hr. The ammonia was allowed to evaporate overnight, the residue was diluted with water, and the amine was isolated with ether and crystallized from aqueous ethanol as needles, m.p. 67–69°, yield 5.0 g.

Anal. Calcd. for $C_{24}H_{27}N$: C, 87.5; H, 8.3; N, 4.3. Found: C, 87.6; H, 8.0; N, 4.4.

The hydrochloride gave needles, m.p. 135–137°, from 2-propanol.

Anal. Calcd. for $C_{24}H_{27}N\cdot HCl\cdot H_2O$: C, 75.1; H, 7.9; N, 3.7. Found: C, 75.6; H, 7.5; N, 3.8.

Esters.—The esters were prepared by holding the alcohol with the appropriate acid anhydride in pyridine at 100° for 16 hr. From several alcohols, inexplicably, no pure ester could be isolated. Those that were prepared are listed in Table IV.

1-Phenyl-2-(2-pyridyl)cyclopropane.—To a solution of sodium (2 g.) in redistilled diethylene glycol (100 ml.) was added redistilled dry hydrazine (10 ml.) and then 2-cinnamylpyridine (5 g.) and the whole refluxed for 1 hr. At this point some of the vapors were allowed to escape until the temperature of the contents of the flask reached 210° when reflux was continued for a further 4 hr. The mixture was cooled, diluted with water (200 ml.), and extracted with four 60-ml. portions of ether. The ether extracts were concentrated and distilled to give the cyclopropane, b.p. 116–120° (0.6 mm.), $n^{20}D$ 1.5990, as a colorless oil; yield 3.3 g.; ultraviolet absorption: λ_{max} ~201, 209 (sh), 229, and 270 mμ (ε ~18,100, 14,000, 14,100, and 6780).

Anal. Calcd. for $C_{14}H_{13}N$: C, 86.1; H, 6.7; N, 7.2. Found: C, 86.0; H, 7.1; N, 7.3.

The base formed a picrate, m.p. 97–102°.

Anal. Calcd. for $C_{14}H_{13}N\cdot C_6H_3N_3O_7$: C, 56.6; H, 3.8; N, 13.2. Found: C, 56.6; H, 4.4; N, 13.4.

Mannich Bases of Indanones.—Of the two indanones used in this work (XII, R = CH_3 and $CO_2C_2H_5$) only the first, 2-methyl-3-phenylindanone, could be made to give Mannich bases. Using dimethylamine and the conditions outlined above for the β-phenylpropiophenones, 2-dimethylaminomethyl-2-methyl-3-phenylindanone, m.p. 72–73° from petroleum ether (b.p. 40–60°), was obtained; yield 55%.

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.7; H, 7.6; N, 5.0. Found: C, 81.7; H, 7.3; N, 4.6.

The hydrochloride had m.p. 189°.

Anal. Calcd. for $C_{19}H_{21}NO\cdot HCl$: C, 72.3; H, 7.0; N, 4.4. Found: C, 72.4; H, 6.9; N, 4.5.

Using morpholine the corresponding 2-methyl-2-morpholinomethyl-3-phenylindanone was isolated as its hydrochloride, m.p. 173–175°, 55% yield.

Anal. Calcd. for $C_{21}H_{23}NO_2\cdot HCl$: C, 70.5; H, 6.8; N, 3.9. Found: C, 70.0; H, 6.7; N, 4.6.

2-(β-Diethylaminoethyl)-2-ethoxycarbonyl-3-phenylindanone.—2-Ethoxycarbonyl-3-phenylindanone (56 g.) in absolute ethanol (400 ml.) was added to a solution of sodium (4.6 g) in absolute ethanol and the mixture boiled under reflux for 2 hr. The stirred cooled solution was then treated with a solution of diethylaminoethyl chloride [freshly prepared by treating the base hydrochloride (80 g.) with 5 *N* NaOH (150 ml.), extracting with cold benzene, and removing the benzene at room temperature *in vacuo*] in absolute ethanol (100 ml.), and the mixture was brought slowly to boiling and boiled under reflux for 1 hr. The solution was filtered, concentrated to a red oil, poured into 2 *N* HCl (250 ml.) and extracted with ether. The aqueous layer was then basified (K_2CO_3) and extracted with ether to give a light brown oil (34 g.). With ethereal HCl this gave a solid, crystallizing from 2-propanol as very small prisms, m.p. 188–190° dec.

Anal Calcd. for $C_{24}H_{29}NO_3\cdot HCl$: C, 69.3; H, 7.3; N, 3.4. Found: C, 69.1; H, 7.2; N, 3.4.

Substituted Indanols (XV).—These compounds were prepared using potassium borohydride or the appropriate Grignard reagent; their physical constants are listed in Table V.

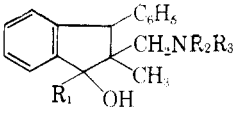
1-Ethylidene-N,N-2-trimethyl-3-phenyl-2-indanmethylamine.—The appropriate tertiary alcohol (**57**) was dehydrated in 84% yield as described above[15] and the substituted ethylene was isolated as the monohydrochloride monohydrate, m.p. 176–180°.

Anal. Calcd. for $C_{21}H_{25}N\cdot HCl\cdot H_2O$: C, 72.9; H, 8.2; N, 4.1. Found: C, 72.9; H, 7.7; N, 4.4.

1-Ethyl-N,N-2-trimethyl-3-phenyl-2-indanmethylamine (63).—The preceding olefin was hydrogenated as described above for

TABLE V

SUBSTITUTED INDANOLS



Compd.	R_1	R_2	R_3	M.p., °C.	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
56	H	CH_3	CH_3	206–208	70	$C_{19}H_{23}NO \cdot HCl \cdot H_2O$[a,b]	68.0	7.8	4.2	68.1	8.0	4.0
57	C_2H_5	CH_3	CH_3	187–200[c]	75	$C_{21}H_{27}NO \cdot HCl$[a]	72.9	8.2	4.1	72.8	8.1	4.2
58	C_6H_5	CH_3	CH_3	250–252	70	$C_{25}H_{27}NO \cdot HCl$[a]	76.2	7.2	3.6	75.9	7.0	3.4
59	$C_6H_5CH_2$	CH_3	CH_3	158–159	45	$C_{26}H_{29}NO \cdot$	84.1	7.9	3.8	84.2	7.6	3.8
60	$C_6H_5CH_2$	CH_3	CH_3	211–212		$C_{26}H_{29}NO \cdot HCl \cdot 0.5C_2H_5OH$[a,d]	75.2	7.7	3.3	75.3	7.6	3.3
61	$C_6H_5CH_2$	$(CH_2)_2O(CH_2)_2$		153–155	72	$C_{28}H_{31}NO_2$	81.3	7.6	3.4	81.5	7.5	3.4
62	$C_6H_5CH_2$	$(CH_2)_2O(CH_2)_2$		204–205		$C_{28}H_{31}NO_2 \cdot HCl$[a]	74.8	7.2	3.1	74.6	7.0	3.1

[a] Hydrochloride. [b] This water of crystallization was lost on drying at 100° under high vacuum for 6 hr. to give product, m.p. 210°. [c] Wide melting point range due to compound being an isomeric mixture. [d] Hemiethanolate.

1-dimethylaminomethyl-1,3-diphenylpentane to give the alkane which was isolated as a mixture of stereoisomeric hydrochlorides, m.p. 203–234°, 88% yield.

Anal. Calcd. for $C_{21}H_{27}N \cdot HCl$: C, 76.5; H, 8.6; N, 4.3. Found: C, 75.9; H, 8.4; N, 4.2.

Pharmacology.—Generally speaking the bases described in this paper showed a spectrum of activity mainly on the central nervous system but, although individual compounds showed an interesting degree of activity, in no case was activity observed sufficiently free from side effects to justify detailed examination. The areas in which activity lay were in the fields of analgesics, anticonvulsants, antiserotonins, and antiarrythmics.

For determining the degree of analgesic activity we relied upon the test of Bianchi and Franceschini[16] where an artery clip is placed at the root of the tail of a mouse; the dose of drug necessary to prevent the mouse from trying to remove the clip or showing signs of pain, by squeaking for example, is then a measure of the analgesic activity of the drug. In some cases analgesia was re-evaluated in rats using the technique of Green, *et al.*,[17] whereby a uniformly increasing pressure is applied to the tip of a rat's tail. In both cases codeine phosphate was the drug used for comparison. Those compounds found active are listed in Table VI.

TABLE VI

ANALGESIC ACTIVITY

Compd.	Mice ED_{50}, mg./kg.[a]	Rats ED_{50}, mg./kg.[a]
4	58	
7	45	
8	30	
10	50	Inactive
12	47	34
14	76	33
19	188	109
37	57	
59	11	5.1
Codeine phosphate	33	3.3

[a] Subcutaneous.

For evaluation of anticonvulsant activity the method of Toman, *et al.*,[18] was employed using fasted mice as the test animal. These were dosed intraperitoneally with the drug and then subjected to a current of 24 mamp. applied for 0.2 sec. through ear clips. For active compounds the end point is the abolition of the extensor component of the convulsion. In Table VII the PD_{50} values are given, which is the dose which will protect 50% of the animals from convulsion. The reference drug used was diphenylhydantoin.

The antiserotonin action of the compounds was determined using the method of Corne, *et al.*[19] 5-Hydroxytryptophan, when injected into mice, produces a characteristic head twitch believed to be due to the presence of excess of 5-hydroxytryptamine in the brain. The dose of the drug required to prevent head twitches in 50% of mice pretreated with 300 mg./kg. of 5-hydroxytryptophan is then determined. The compounds chosen for comparison were chlorpromazine and morphine. Results are listed in Table VIII.

Finally, the antiarrythmic action was evaluated using the method of Angelakos and Hegnauer[20] whereby the drugs' activity

TABLE VII

ANTICONVULSANT ACTIVITY

Compd.	Mice PD_{50}, mg./kg.[a]
1	25
3	45
7	50
9	63
14	63
52	50
57	63
63	25
Diphenylhydantoin	40–50

[a] Intraperitoneally.

TABLE VIII

ANTISEROTONIN ACTIVITY

Compd.	Mice ED_{50}, mg./kg.[a]
14	0.50
16	1.75
17	1.56
37	12.5
41	2.55
46	2.0
Chlorpromazine	0.86
Morphine	1.60

[a] Intraperitoneally.

TABLE IX

ANTIARRYTHMIC ACTIVITY

Compd.	Dogs ED_{50}, mg./kg.[a]
4	16–32
8	24–32
9	28–32
14	24–32
23	28–32
43	24–32
53	12–16
Quinidine sulfate	28–32

[a] Cumulative intravenous dose.

(16) C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9**, 280 (1954).

(17) A. F. Green, P. A. Young, and E. I. Godfrey, *ibid.*, **6**, 572 (1951).

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

(19) S. J. Corne, R. W. Pickering, and B. T. Warner, *Brit. J. Pharmacol.*, **20**, 106 (1963).

in lessening the ventricular fibrillation induced in anesthetized dogs by immersion tank hypothermia was measured. Quinidine was the reference drug used and the active compounds are listed in Table IX.

(20) E. T. Angelakos and A. H. Hegnauer, *J. Pharmacol. Exptl. Therap.*, **127**, 137 (1959).

Acknowledgment.—The authors thank Dr. R. E. Bowman for many helpful discussions, Mr. F. H. Oliver for the microanalyses, Miss E. M. Tanner for the physical measurements, Dr. Vandenbelt for the n.m.r. spectra, and Drs. Corne, Chen, and Wheelock, and Mr. C. Schneider for the pharmacological testing.

New Analgesic N-Substituted Carboxamides

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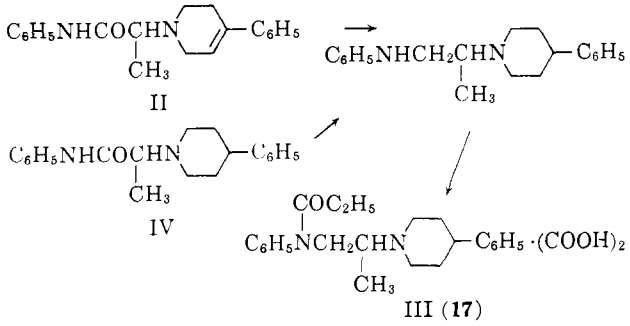
A series of N-substituted propionanilides was synthesized as potential analgesics. The most active compound, N-[1-methyl-2-(4-hydroxy-4-phenylpiperidino)ethyl]propionanilide oxalate (**27**), was approximately 150 times more active than morphine by the artery-clip assay method in mice.

In the course of our search for new, potent analgesics, we have synthetized a group of N-substituted carboxamides (I), mainly N-substituted propionanilides, which are structurally related to methadone in that the quaternary carbon atom and a phenyl group of methadone are replaced with a tertiary nitrogen. During the course of our work, two potent analgesics, phenampromid and diampromid,[1] were reported. Both compounds are N-substituted propionanilides. Similar compounds were described later by Shigematsu[2] and by Carabateas.[3] Among our compounds, **1** and **2** of Table I were described in a recent patent.[4]

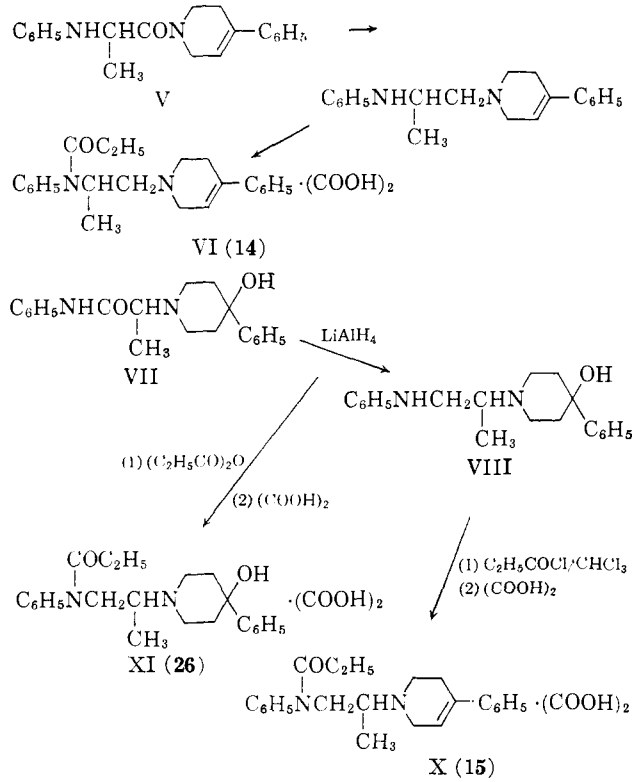
The compounds reported here are listed in Table I and may be represented by the generic formula R^1-$C_6H_4(CH_2)_nN(COR^2)CHR^3CHR^4$+B (I). The isomerically pure compounds were prepared readily by reduction of the corresponding amides, with lithium aluminum hydride followed by acylation. When α-(1,2,3,6-tetrahydro-4-phenyl-1-pyridyl)propionanilide (II) was reduced in this way, followed by propionylation, the product isolated as the oxalate was unexpectedly the saturated compound (III). The latter was also synthesized by reducing α-(4-phenylpiperidino)propionanilide (IV), followed by propionylation and formation of the oxalic acid salt.

Salts (III), prepared by both routes, were identical by mixture melting point determination and gave identical ultraviolet spectra which showed two maxima at 257.5 mμ (ε 1050) and 264 mμ (ε 832).



III (**17**)

In contrast, the reduction of 1-(α-anilinopropionyl)-1,2,3,6-tetrahydro-4-phenylpyridine (V), an isomer of II, gave the unsaturated compound VI. In support of the unsaturated structure was a strong absorption maximum at 244.5 mμ (ε 14,600),[5] indicating the presence of a double bond conjugated with the aromatic ring. It is reported that a double bond in the systems ArC=CCO— or ArC=CN—[6] may be reduced with lithium aluminum hydride, but such a reduction of the double bond in the grouping $C_6H_5C{=}CCH_2$— has not been described previously.



(1) W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, **81**, 1518 (1959); *J. Org. Chem.*, **25**, 1033 (1960); *ibid.*, **26**, 476, 485 (1961).

(2) N. Shigematsu, *Yakugaku Zasshi*, **81**, 423 (1961); *ibid.*, **81**, 815 (1961); N. Sugimoto, K. Okumara, N. Shigematsu, and G. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **10**, 1061 (1962); G. Hayashi, N. Shigematsu, and Y. Kowa, *Yakugaku Zasshi*, **81**, 62 (1963).

(3) P. M. Carabateas, W. F. Wetterau, and L. Grumbach, *J. Med. Chem.*, **6**, 355 (1963).

(4) O. E. Fancher and S. Hayao, U. S. Patent 3,037,982 (June 5, 1962).

(5) α-Methylstyrene has λ_{max}^{EtOH} 243 mμ (ε 11,500); A. E. Gillam and E. S Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," 2nd Ed., Edward Arnold Ltd., London, 1957, p. 277.

(6) W. G. Brown, *Org. Reactions*, **6**, 480 (1951).