[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

ANTIMALARIALS. α-PHENYL-β-DIALKYLAMINO ALCOHOLS[1]

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This investigation had its beginning in the fall of 1942 as a part of the cooperative effort initiated by the Division of Chemotherapy of the National Institute of Health under Dr. L. F. Small (1) and it was continued into the summer of 1944 at which time, although not completed, it was interrupted because of the greater promise and urgency of other problems. It was based on convincing evidence that the α-aryl-β-*tert.*-amino alcohol system is the structural feature of quinine which is chiefly responsible for its antimalarial activity; it had been shown that the quinuclidine ring system is not essential for this activity and can be replaced by non-cyclic secondary or tertiary amino groups, and also that the quinoline nucleus is not essential and can be replaced by other aryl nuclei such as the naphthyl and tetrahydrophenanthryl (*cf.* 1, 2, 3, 4, 5).

The first compounds made of the α-phenyl-β-dialkylaminoethanol type (IA) carried the following as the benzenoid groups: *p*-isopropylphenyl, carvacryl, *p*-cyclohexylphenyl, *p*-benzylphenyl, and *p*-bibenzyl. These compounds were made in order to test the effectiveness of the simple phenyl nucleus when it was so weighted with substituents as to bring the molecular weight to a level comparable with that of quinine and other active drugs.

The first compound found which possessed significant antimalarial activity was α-4-chlorophenyl-β-diamylaminoethanol (IIAd).[4] The dioctylamino analog (IIAh) which was made later showed still higher activity. These compounds had been made with two points in mind, one, the possible activating influence of the *p*-chlorine, and the other, the partial compensation for the low molecular weight of the nucleus (as compared with that of quinine and Atabrine) by the use of this nuclear substituent and by the use of the long-chain N,N-dialkyl

[1] The larger portion of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia.

The completion of the manuscript and a few of the experiments and analyses were carried out with assistance from a grant-in-aid from the National Institute of Health to the University of Virginia.

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[3] Assisted by Philip Francis duPont Fellowships, 1942-1944.

[4] Submitted for testing February 13, 1943.

groups. The activity of these compounds was on the order of one-quarter of that of quinine and this finding, surprising at the time, stimulated the extensive investigation of a large variety of analogs to evaluate the effect of (a) the phenyl nucleus itself; (b) as many variations as possible in the alkyl groups on nitrogen; (c) the variation in nuclear halogen from fluorine, chlorine, and bromine to iodine; (d) the substitution of other groups, notably alkyl and alkoxyl; (e) the relative effect of the ortho, meta, and para positions of the substituent, especially the ortho and para where the electron displacements are similar in a degree to that in quinine; (f) the insertion of two or more substituents, including alkyls and alkoxyls, in as many different arrangements as could quickly be produced from easily accessible materials; (g) the lengthening of the amino alcohol chain, $-CH(OH)-CH(NR_2)-(CH_2)_nCH_3$, where n = 0, 1, 3, and 9; and (h) the separation of the alcoholic hydroxyl and dialkylamino group by one extra carbon, involving the type, $-CH(OH)CH_2CH_2NR_2$. The work covered fifty different nuclear variations and over sixty variations in the N,N-dialkyl groups; and it involved the preparation of a total of 184 amino alcohols which are listed in Table I (6), together with fifty-five amino ketones (also listed in Table I) which were isolated for purposes of comparison.

RESULTS OF ANTIMALARIAL TESTS

It is clear from the quinine equivalents listed in Table I that a considerable proportion of the many types of α-phenyl-β-amino alcohols and the corresponding ketones are moderately or slightly active against avian malaria. The series most extensively explored was the *p*-chlorophenyl, and here, with one outstanding exception, most of the dialkylamino and benzylalkylamino alcohols within certain ranges of molecular weight showed consistent antimalarial activity of a modest order ranging from below one-tenth to one-quarter of that of quinine. The exception was the diisooctylamino compound (di-2-ethylhexyl) (IIAi) which proved to be inactive in contrast to the moderately active di-*n*-octylamino isomer (IIAh).

Little indication appeared of any significant or striking group-positional effect upon the activity, and it is noteworthy that, in spite of the steric hindrance involved, α-2,6-dichlorophenyl-β-dioctylaminoethanol (XXIX) was moderately active.

The activities of the amino ketones tested in most cases were of the same order of magnitude as those of the corresponding amino alcohols.

With a few exceptions in a long list of examples the amino alcohols and ketones based on morpholine and on piperidine proved to be inactive.

It was only toward the end of this program of research, with the benefit of experience and knowledge in the matter of the favorable balance of nuclear substituents and molecular weight as modified by N,N-dialkyl groups, that the most active drugs were found.

Special mention should be made of the following α-phenyl-β-dioctylaminoethanols each of which proved to be equal to or better than quinine in at least one test against avian malaria; namely, those with the nuclear substitutions: 3,4-dichloro (XXV), 2,4-dichloro (XXVI), 2,5-dichloro (XXVII), 2-methyl-4,5-dichloro (XXXIV), and 4-*n*-hexyl (XIII). It is along these lines of substitution in the nucleus, and others suggested by the results described in this paper, that some further work is now being undertaken in order to find the upper limits of antimalarial activity which may be possible in this type of compound.

SYNTHETIC METHODS

Most of the drugs were made by the following transformations: condensation of the bromomethyl ketone with the appropriate secondary amine to give the *tert.*-aminomethyl ketone, and reduction by means of aluminum isopropoxide to the amino alcohol (8).[4]

$$\mathrm{Ar{-}COCH_2Br} \rightarrow \mathrm{Ar{-}COCH_2NR_2} \rightarrow \mathrm{Ar{-}\underset{\displaystyle OH}{\underset{|}{C}}HCH_2NR_2}$$

An alternative path, used in a few cases only, was reduction of the bromomethyl ketone to the bromohydrin and condensation of this with the appropriate secondary amine (8, 9, 10).

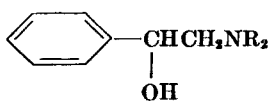
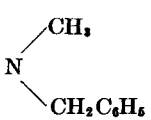
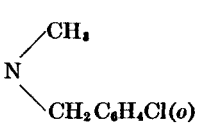
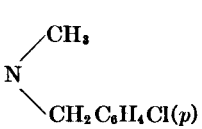
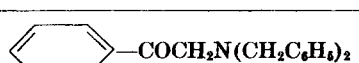
$$\mathrm{Ar{-}COCH_2Br} \rightarrow \mathrm{Ar{-}\underset{\displaystyle OH}{\underset{|}{C}}HCH_2Br} \rightarrow \mathrm{Ar{-}\underset{\displaystyle O}{CH{-}{-}CH_2}} \rightarrow \mathrm{Ar{-}\underset{\displaystyle OH}{\underset{|}{C}}HCH_2NR_2}$$

Those bromomethyl ketones which were not available as starting materials were for the most part made by bromination of the methyl ketones in ether as the solvent, but in a few cases they were made from the acids *via* the now widely used path through the acid chloride and the diazomethyl ketone (5). The methyl ketones, when not available, were usually made from the substituted aromatic hydrocarbons by the Friedel-Crafts reaction; a few were made through the addition of methylmagnesium iodide to the appropriate nitrile; and one was made from the aldehyde by addition of methylmagnesium iodide and oxidation of the resulting alcohol to the ketone.

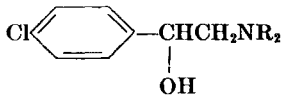
Much of the work here reported was done before the efficacy of the synthetic path through the bromohydrin was realized, and doubtless the yields in many of these syntheses could be greatly improved by the use of the latter procedure. Throughout this investigation the governing objective was to prepare as wide a variety as possible of new types of drugs in sufficient quantity and purity for adequate screening tests, and to prepare them as quickly as possible; consequently, once samples were tested and found to be without further interest, no more work was done on preparative details, derivatives, and intermediates, nor toward securing other data normally desirable for recording. Many short cuts in syntheses were taken and the isolation of intermediates often was omitted for the sake of the saving of time. The necessarily limited data accumulated

TABLE I

THE α-PHENYL-β-DIALKYLAMINO ALCOHOLS AND CORRESPONDING KETONES

NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR $n_D^{20°}$	B.P. OR M.P., °C.[f]
IA							
a	4666	N(*n*-octyl)$_2$	<0.06	5R;3K	13	1.4830	200–203/1 mm.
b	8346	N(*n*-nonyl)$_2$	0.06	5R;4K	26	1.4847	225–227/4 mm.
c	8118		<0.06	6R;3L	7[n,i]	1.5610–1.5613	171–173/1 mm.
d	8889		<0.1	5R;3K	—	$1.5675^{25°}$	167–168/2 mm.
e	8413		<0.1	5R;3K	28	1.5690–1.5693	187–190/2 mm.
f	6749	N($CH_2C_6H_5$)$_2$·HCl	<0.03	8UW;3N	65	abs. EtOH-*i*PrOH[i]	213
IB							
	6548		—[w]	Ref. 13	71	ethanol	80–82[w]

IIA



a	9517	$N(CH_2CH_3)_2$	<0.1	7R;3M	53	1.5190	117–119/2 mm.
b	4914	$N(CH_2CH_2CH_2CH_3)_2$	sl.act.[b,3]	5TR;3K	38	$1.5026^{26°}$	162–165/2 mm.
b_1	—	b-hydrochloride	—	Q	—	—	98–99
c	7210	$N\left[CH_2CH(CH_3)(CH_3)\right]_2$	<0.06	7R;3FM	67	1.5021	166–167/1 mm.
d	3097	$N(CH_2CH_2CH_2CH_2CH_3)_2$	0.3	5TR;4K	59	1.4990	160–162/2 mm.
e	8475	$N\left[CH_2CH_2CH(CH_3)(CH_3)\right]_2$	0.1	5TR;4K	51	1.4979–1.4980	160–162/3 mm.
f	6418	N(*n*-hexyl)$_2$	<0.3	9R;3K	36	$1.4951^{28°}$	170–171/1 mm.
g	8302	N(*n*-heptyl)$_2$·HCl	<0.06	5RQ;4K	20	ethyl acetate	87–88
h	4067	N(*n*-octyl)$_2$	1.0/(0.3)[b,1]	11R;5R	52[k]	$1.4941^{25°}$	222/2 mm.
h_1	—	h-hydrochloride	—	5RQ;3K	—[k]	EtOH-H_2O	86–87
i	5419	$N\left[CH_2CH((CH_2)_3CH_3)(CH_2CH_3)\right]_2$	<0.03	5R;3K	65	1.4960	184–189/2 mm.

TABLE I *con't.*

NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n_D^{20}[e]	B.P. OR M.P., °C.[f]
j	7485	N(*n*-nonyl)$_2$	0.1	7R;4M	18	1.4912–1.4914	216–218/2 mm.
k	8290	N(*n*-decyl)$_2$	0.1	5R;4K	37	1.4898–1.4900	245–246/1.8 mm.
l	8133	N(*n*-undecyl)$_2$	<0.03	5R;3K	43	1.4899–1.4902	228–230/2 mm.
l_1	—	l-hydrochloride	—	Q	—	ethyl acetate	86–88
m	9019	N(*n*-dodecyl)$_2$	<0.03	5S;3K	—[k]	1.4881–1.4900	—[k]
m_1	—	m-hydrochloride	—	Q	—	—	79–82[u]
n	8826	N(*n*-tridecyl)$_2$	<0.03	5S;3K	20	1.4872–1.4880	—[k]
o	4915	$N(CH_3)(CH_2C_6H_5)\cdot HCl$	0.06	5TR;3K	54	abs. ethanol	166–167
p	8296	$N(CH_2CH_3)(CH_2C_6H_5)$	0.06	7R;3M	38	isopropyl ether	57–58[s]
q	6754	$N(CH_2CH_2CH_3)(CH_2C_6H_5)$	0.06	5S;4K	58	ethanol	44–45

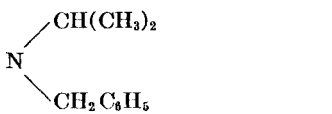
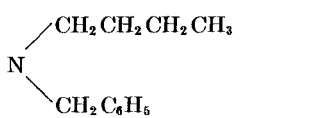
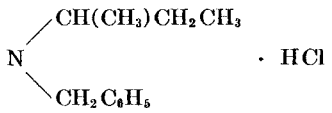
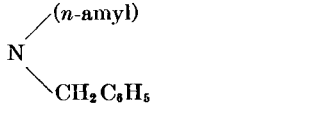
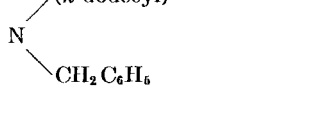
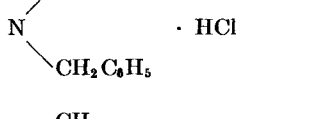
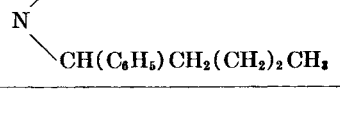
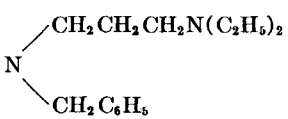
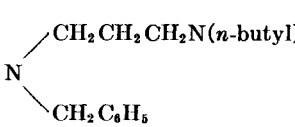
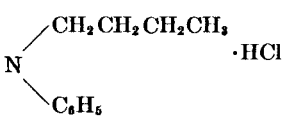
r	8299		0.03	6U;4L	56	ethanol	65–67
r_1	—	r-hydrochloride	—	W	—	isopropanol	185–186
s	5044		0.06	5R;3K	—	ethanol	49–50[a]
t	8301		0.06	6Q;3GL	44	acetone	176–179
u	8128		0.1	5R;3K	30	$1.5424^{26°}$	209–212/2 mm.[a]
v	7983		0.03+	5R;4K	47	—[k]	56–57
w	8382		<0.15	6Q;3L	15	butanone	190–192 dec.
x	6747		<0.06	5R;4K	49	1.5512	197–198/1 mm.

TABLE I *con't.*

NO.	SN[a]	TYPE FORMULA $-NR_2$	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n_D^{20}	B.P. OR M.P., °C.[f]
y	6974	$N(CH_3)(CH_2C_6H_4Cl(p)) \cdot HCl$	0.06	7RQ;3G	53	acetone	161–162
z	8477	$N(CH_3)(CH_2C_6H_4OCH_3(p)) \cdot HCl$	0.06	5Q;3K	66	1:10-EtOH-EtOAc	150–152
aa	8479	$N(n\text{-butyl})(CH_2C_6H_4OCH_3(p))$	0.06	6TU;3L	39	75% ethanol	55[g]
bb	—	$N(CH_2C_6H_5)_2$	—	—	—	70% ethanol	97–98
bb_1	5050	bb-hydrochloride	0.3	9TQ;3K	55	CH_3OH-ether	200.5–202
cc	8181	$N(CH_2CH_3)(CH_2\text{-}\alpha\text{-furyl})$	<0.06	7R;3GM	32	1.5423	176/10 mm.
dd	9018	$N(CH_3)(CH_2\text{-}\alpha\text{-naphthyl}) \cdot HCl$	<0.04	6Q;3L	—	isopropanol	189–190

ee	7389		<0.3	5R;4K	17	1.5453	219–221/4 mm.
ff	8982		<0.1	5R;4K	28	1.5354–1.5360	241–243/1 mm.
gg	—	tetrahydroisoquinolyl	—	—[k]	—[k]	pet. ether	90.5–91
gg$_1$	4912	gg-hydrochloride	<0.06	—[k]	—[k]	water	229–231[e]
hh	4913	tetrahydroquinolyl	<0.1	8TR;3FN	28	$1.6121^{29°}$	223–227/3 mm.
ii	7981	morpholinyl	<0.1	8TU;3GN	79	ligr.-*i*PrOH	78–80
jj	7198	2-methylmorpholinyl[m]	<0.1	6T;3GL	31	ligroin	86–87
kk	7197	2,6-dimethylmorpholinyl	<0.06	6R;3GL	25	$1.5292^{25°}$	169–170/1 mm.
ll	8849	2-(*n*-hexyl)piperidyl	<0.1	11R	53	1.5248–1.5249	150–169/2 mm.
mm	7517	*trans*-dodecahydrocarbazyl	<0.1	7TR;3M	47	80% ethanol[h]	81–82
nn	8398		<0.02	6Q;3GL	12	acetone-ether	145–146 dec.

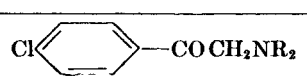
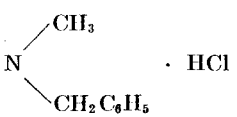
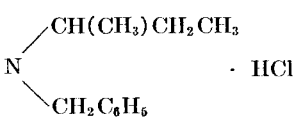
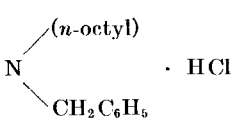
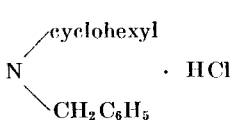
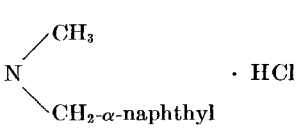
IIB 

TABLE I *con't.*

NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n_D^{20c}	B.P. OR M.P., °C.[f]
a	—	$N(CH_2CH_3)_2 \cdot HCl$	—	3FL	—	ethanol-ether	158–159[v]
b	6645		0.06	3L	60	butanone	188–191
c	—		—	3GL	60	*i*PrOH-butanone	167–170
d	7398		0.02	3FL	—	EtOAc-ethanol	167–169[u]
e	—		—	3L	44	acetone	185–186 dec.
f	—		—	4L	60	ethanol	202–203
g	6644	tetrahydroisoquinolyl	<0.06	3FN	63	ethanol	100[v]
h	—	morpholinyl	—	—	—	ligroin	79–80[u]

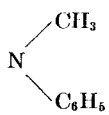
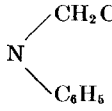
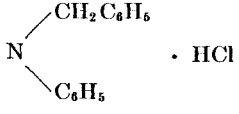
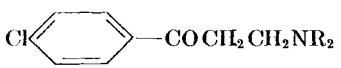
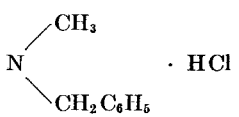
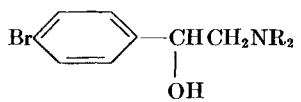
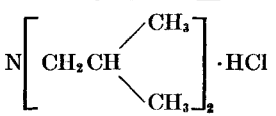
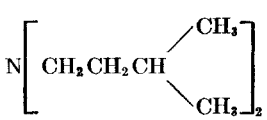
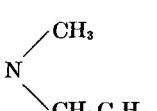
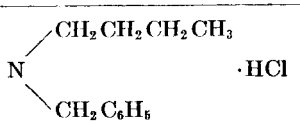
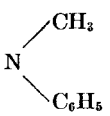
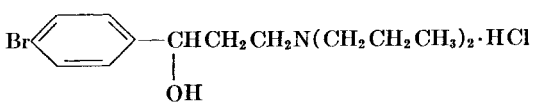
h_1	6641	h-hydrochloride	<0.1	3GL	59	ethanol	227–228 dec.
i	7387	2-methylmorpholinyl·HCl	<0.06	3GL	77	isopropanol	208–210 dec.
j	6640	2,6-dimethylmorpholinyl ·HCl	<0.06	3GL	41	isopropanol	219–221 dec.
k	6661		<0.03	Ref. 7	36	ethanol	109–110
l	6667		<0.03	3N	50	ethanol	85–86[a]
m	8127		<0.02	3NP	62	isopropanol	163–164
n	—	tetrahydroquinolyl	—	3FN	55	ethanol	106–108
IIC							
a	—	N(*n*-amyl)$_2$·HCl	—	—[k]	67[n]	acetone-ether	100–103
b	7393		<0.06	—[k]	63[n]	ethanol	170–172

TABLE I *con't.*

NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n_D^{20}[e]	B.P. OR M.P., °C.[f]
IIIA							
a	7205		<0.03	5Q;3K	25	acetone-ether	142.5
b	4911	$N(CH_2CH_2CH_2CH_2CH_3)_2$	0.3	5TR;4K	52	1.5120	166/2 mm.
c	8933		0.1	5TR;4K	65	1.5091–1.5092	155–157/2 mm.
d	8396	N(*n*-hexyl)$_2$	<0.3	5TS;3K	40	1.5069–1.5073	180–181/1 mm.
e	8300	N(*n*-heptyl)$_2$·HCl	<0.15	5Q;4K	62	ethyl acetate	96.4
f	8367	N(*n*-octyl)$_2$	0.06	5TR;3K	14	1.4991–1.4992	210–212/1 mm.
g	7112	N(*n*-nonyl)$_2$	0.3	7R;3M	45	1.4990	235–239/1 mm.
h	7204	 ·HCl	0.06	6Q;3L	60	ethanol-ether	175–176

i	8397		0.15	5Q;3K	39	ethyl acetate	125–127
j	7196	morpholinyl	<0.06	8TU;3GN	50	ligroin	87.5–88.5
k	7980	2-methylmorpholinyl[m]	<0.06	6U;3GL	29	ligroin	94–95
l	8132	2-ethylmorpholinyl·HCl	<0.06	6TQ;3GL	52	CH_3OH-*i*PrOH	186–187
m	8130	3-ethylmorpholinyl·HCl	<0.06	7TUQ;3GM	33	acetone	141–143
n	7979	2,6-dimethylmorpholinyl·HCl	<0.06	6RQ;3GL	35	isopropanol	193 dec.
o	8131	3,3-dimethylmorpholinyl·HCl	<0.06	8T;3N	43	ethanol	241–242 dec.
p	7917	*trans*-decahydroquinolyl·HCl	<0.06	8T;4N	56	isopropanol	234–236[o]
q	—		—	8R;3N	33	1.6135	195–197/3 mm.

IIIB 

	—		—	—[k]	—[i]	acetone	162–164

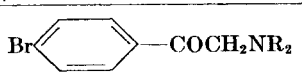
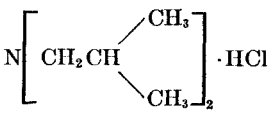
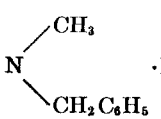
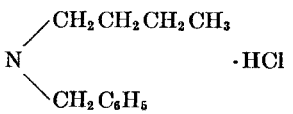
IIIC 

TABLE I *con't.*

NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n_D^{20}[e]	B.P. OR M.P., °C.[f]
a	7206		<0.03	3L	29	ethyl acetate	139–140[u,w]
b	6643		0.06	3L	71	ethanol-ether	190–191
c	7397		0.06	3L	20	*i*PrOH-ether	166
d	—	morpholinyl	—	Ref. 19	78	isopropanol	91–92
d_1	7391	d-hydrochloride	<0.1	Ref. 19	52	ethanol	223–224 dec.
e	7390	2-methylmorpholinyl·HCl	<0.15	3GL	66	1:6-CH_3OH-*i*PrOH	231–232 dec.[v]
f	—	2-ethylmorpholinyl·HCl	—	3GL	82	ethanol	228 dec.[v]
g	7978	2,6-dimethylmorpholinyl·HCl	<0.06	3GL	58	isopropanol	235–236 dec.[v]
h	—	3,3-dimethylmorpholinyl	—	3N	49	isopropanol	73–74[u,w]
h_1	—	h-hydrochloride	—	3P	—	ethanol	232 dec.[v]

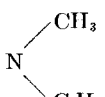
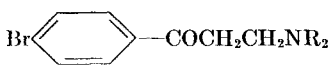
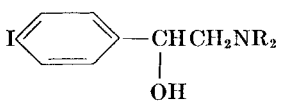
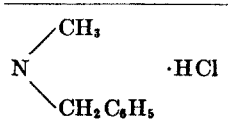
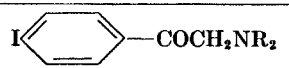
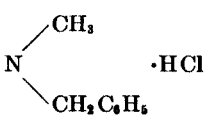
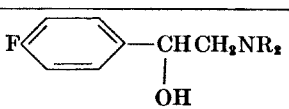
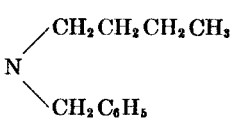
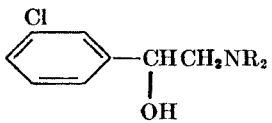
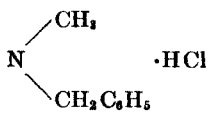
i	6545	*trans*-decahydroquinolyl	<0.1	4N	77	88% ethanol	77.5–78
j	7258		<0.03	3N	36	ethanol	105–106
IIID							
a	13361	N(*n*-propyl)$_2$·HCl	<0.06	—[k]	55[n]	*i*PrOH-ether	128–130
b	8981	N(*n*-butyl)$_2$·HCl	0.06	—[k]	30[n]	*i*PrOH-ether	133–135
IVA							
a	7203	N(ethyl)$_2$·HCl	0.06	6Q;3L	—[i]	EtOH-ether	181–184
b	7201	N(*n*-propyl)$_2$·HCl	sl.act.[b,3]	6Q;3L	—[i]	EtOH-ether	196–197
c	7200	N(*n*-butyl)$_2$·HCl	0.15	6Q;3L	—[i]	EtOH-ether	134–136
d	8184	NH-*n*-butyl·HCl	0.3	6Q;3L	65	EtOH-ether	183–186
e	5030	N(*n*-amyl)$_2$·HCl	<0.3	7Q;3M	35	$CHCl_3$-ether	99.5–101
f	—	N(*n*-octyl)$_2$	—	7R;3M	38	$1.5136_{30}°$	230–236/1 mm.[u]
f_1	9514	f-hydrochloride	0.2	Q	—	EtOAc-pet.ether	91–93

TABLE I *con't.*

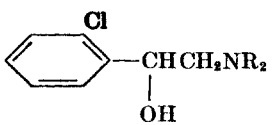
NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n_D^{20}[e]	B.P. OR M.P., °C.[f]
g	7199	 ·HCl	<0.06	6Q;3L	—[i]	EtOH-ether	185–187
h	7202	piperidyl·HCl	<0.06	6Q;3L	—[i]	EtOH-ether	249–251
IVB							
a	7395	N(*n*-propyl)$_2$·HCl	0.06	3L	89	EtOH-ether	180–186[g]
b	7394	N(*n*-butyl)$_2$·HCl	0.06	3L	82	EtOH-ether	207–208 dec.
c	6642	 ·HCl	0.03	3L	77	EtOH-ether	209–211[g]
d	7396	piperidyl·HCl	<0.06	3L	55	EtOH-ether	250–251 dec.
V							
a	7212	N(*n*-octyl)$_2$	0.06	5R;3K	56	1.4780	196/1 mm.
b	8414	N(*n*-nonyl)$_2$	0.1	5R;3K	37	1.4780	232–233/1 mm.
c	7211		0.06	5R;3K	66	1.5305	173.5/1 mm.

VI



a	8125	N(*n*-octyl)$_2$	0.1	5S;3K	22[n]	1.4958	238–242/10 mm.
b	8122		0.15	6Q;3L	26[n]	acetone	159–160

VII



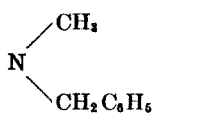
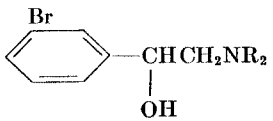
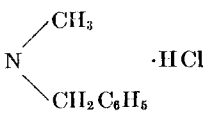
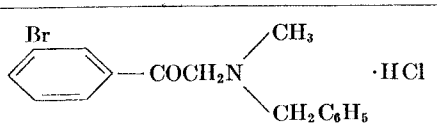
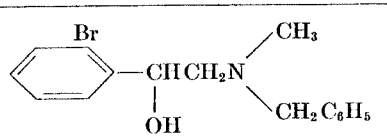
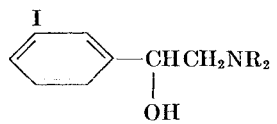
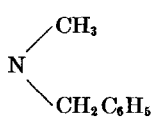
a	—	N(*n*-amyl)$_2$	—	5R;3K	53	1.5000	160–171/0.5 mm.[a]
a$_1$	6755	a-hydrochloride	<0.15	Q	40	EtOH-ether	92–93.5
b	6748	N(*n*-octyl)$_2$	0.1	5R;3K	43	1.4928	218–219/2 mm.
c	—		—	5R;3K	72	1.5692	163–164/1 mm.[a]
c$_1$	8126	c-hydrochloride	0.06	Q	63	EtOH-ether	127–129

TABLE I *con't.*

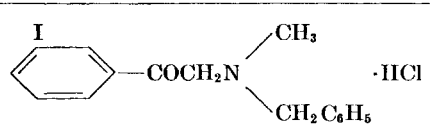
NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n_D^{20}[e]	B.P. OR M.P., °C.[f]
VIIIA							
a	8498	N(*n*-butyl)$_2$·HCl	0.15	5RQ;3K	—	EtOH-ether	146
b	8124	N(*n*-amyl)$_2$	0.1	5R;3K	30	1.5138	178–180/4 mm.
c	8123		0.15	6Q;3L	36	*i*PrOH-ether	181
VIIIB							
	—		—	3L	60	ethanol	200
IX							
	8939		<0.1	7R;3M	59	1.5826–1.5839	172–175/2 mm.

XA



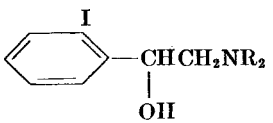
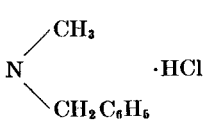
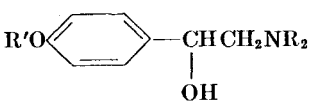
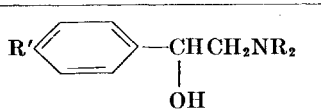
a	9040	$N(CH_3)_2$	0.04	5R;3K[p]	26	1.5872	132–133/2 mm.
b	—	N(ethyl)$_2$	—	7R;3M	68	1.5661	149.5/3 mm.[u]
b_1	8499	b-hydrochloride	0.15	Q	43	EtOH-ether	105–108
c	—	N(*n*-propyl)$_2$	—	7R;3M	56	1.5502	166–167/3 mm.[u]
c_1	8183	c-hydrochloride	0.15	Q	49	EtOH-ether	130–133
d	—	N(*n*-butyl)$_2$	—	7R;3M	58	1.5399	190/4 mm.[u]
d_1	8182	d-hydrochloride	0.15	Q	48	EtOH-ether	127–128
e	—		—	6R;3L	56	1.6075	195/2 mm.[u]
e_1	9042	e-hydrochloride	0.06	Q	45	EtOH-ether	173–176

XB



	8347		0.06	3L	97	EtOH-ether	199–204

TABLE I *con't.*

NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n_D^{20}[e]	B.P. OR M.P., °C.[f]
XI							
a	9038	N(ethyl)$_2$·HCl	0.1	7RQ;3M	26	EtOH-ether	171–174[g]
b	9024	N(*n*-propyl)$_2$·HCl	<0.15	5RQ;3K	23	EtOH-ether	143–145
c	9022	N(*n*-butyl)$_2$·HCl	<0.06	5RQ;3K	20	EtOH-ether	117–120[g]
d	9026		0.04	7SQ;3M	25[h]	EtOH-ether	156–159
XII			(a) R′ = —CH_3; (b) R′ = —CH_2CH_3; (c) R′ = —$CH_2CH_2CH_2CH_3$				
a	2585	N(*n*-amyl)$_2$	<0.3	5TS;3K	30[n]	1.4958	182–191/2 mm.
b	3103	N(*n*-amyl)$_2$	<0.3	5TR;3K	25[n]	1.4953	202–206/2 mm.
c	3104	N(*n*-butyl)$_2$	<0.3	5TR;3K	20[n]	1.4950	200–205/2 mm.
XIII			(a,b) R′ = isopropyl; (c,d) R′ = *n*-hexyl; (e,f) R′ = cyclohexyl; (g) R′ = *n*-decyl; (h) R′ = *n*-dodecyl.				

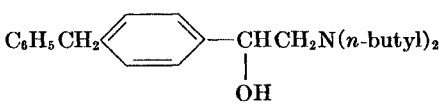
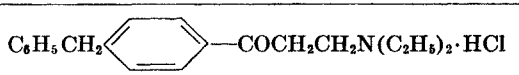
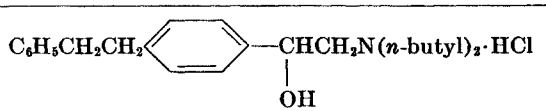
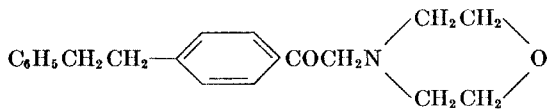
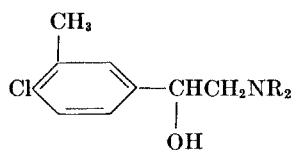
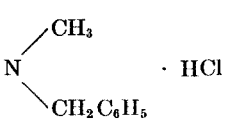
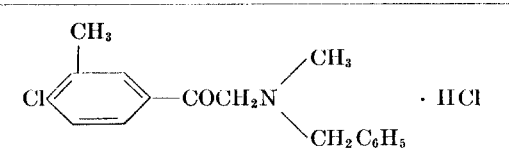
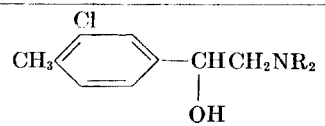
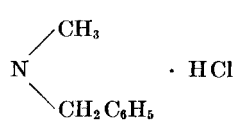
a	2586	N(*n*-butyl)$_2$	<0.3	5R;4K	24[n]	1.4964	214–215/14 mm.
b	3108	N(*n*-amyl)$_2$	<0.1	5R;4K	26[n]	—	206/4 mm.
c	8842	N(*n*-amyl)$_2$	0.04	5S;4K	39[n]	1.4897	—[k]
d	8838	N(*n*-octyl)$_2$	0.3 (2.0)[b2]	5R;4K	34[n]	1.4867	245–258/ 2. mm
e	3550	N(ethyl)$_2$	<0.3	5R;4K	34[n]	EtOH-H_2O	59–60
f	3109	N(*n*-butyl)$_2$	<0.1	5R;4K	41[n]	—	229–230/6 mm.
g	8839	N(*n*-butyl)$_2$	<0.3	5S;4K	14[n]	1.4894	—[k]
h	9830	N(ethyl)$_2$	<0.6	5S;4K	31[n]	1.4962	200–220/2 mm.
XIVA							
	2747		<0.3	5R, 3G	9[n]	1.5340	217–218/2 mm.
XIVB							
	—		—	—[k]	34[n]	$CHCl_3$-ether	105–106.5[l]
XVA							
	3542		<0.3	5Q;3F[k]	40[k]	EtOAc or H_2O	118.5–119

TABLE I *con'l.*

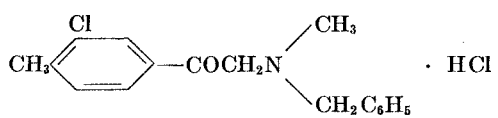
NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n_D^{20}[e]	B.P. OR M.P., °C.[f]
XVB							
	3546		<0.06	3N	57	ethanol	119–120
XVIA							
a	6656	$N(n\text{-amyl})_2$	<0.3	—[k]	36	1.5040[24°]	196–200/2–3 mm.
b	7208	$N(n\text{-octyl})_2$	0.06	5R;3K	13[n]	1.5051–1.5061	216–221/0.5 mm.
c	7207		<0.06	6Q;3L	18[i,n]	abs. EtOH-ether	188–189
XVIB							
	7392		0.06	3L	24[n]	abs. EtOH-ether	196–197

XVIIA



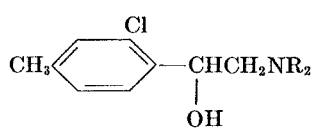
a	8860	N(*n*-amyl)$_2$	<0.1	7R;3M	30^n	1.5047	175–177/1 mm.
b	8895	N(*n*-octyl)$_2$	0.3	7R;3M	34^n	1.5065	210–215/1 mm.
c	8892		<0.02	6Q;3L	37^n	abs. EtOH-ether	188–191

XVIIB



	—		—	3L	45^n	abs. EtOH-ether	185–187

XVIII



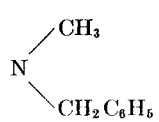
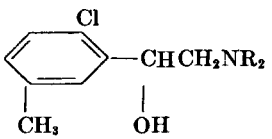
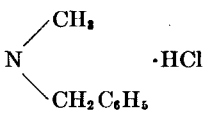
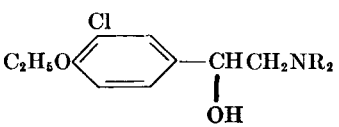
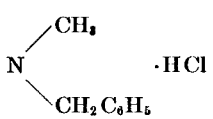
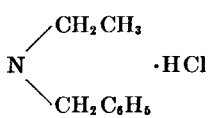
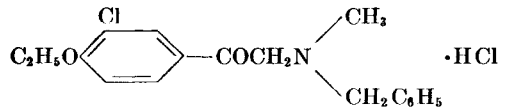
a	7209	N(*n*-amyl)$_2$	0.3	5R;3K	22^n	1.5034–1.5037	183–185/0.5 mm.
b	8611		0.1	6R;3L	10^n	1.5664–1.5669	194–196/ 1 mm.

TABLE I *con't.*

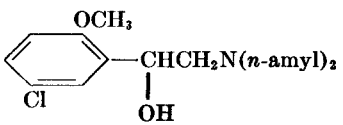
NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n_D^{20}[e]	B.P. OR M.P., °C.[f]
XIX							
a	9515	N(*n*-octyl)$_2$	0.6	9SR;3K	5[n]	1.4967	238–240/2 mm.
b	8506		0.15	6Q;3L	23[n]	acetone	144–145
XXA							
a	6973	N(ethyl)$_2$.HCl	<0.15	5Q;3HK	55	EtOH-ether	148–149
b	7195	N(*n*-amyl)$_2$.HCl	<0.3	6Q;3L	23	EtOH-ether	95–96
c	7194		<0.06	6Q;3L	46[i]	EtOH-ether	196–197
d	7193		0.03	6Q;3L	30	EtOH-ether	146–147

XXB



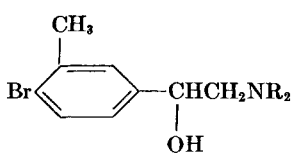
	7975		<0.06	3L	51	EtOH-ether	193–194

XXI



	—		—	5R;3JK	77	1.5050	180/1 mm.[u]
	8612	hydrochloride	0.15	Q	—	ether	165–167

XXII



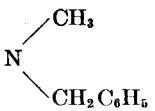
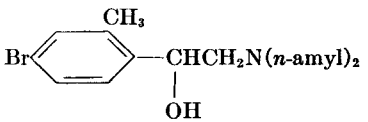
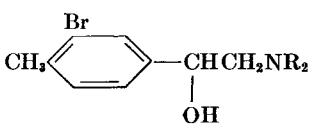
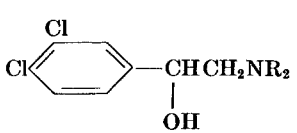
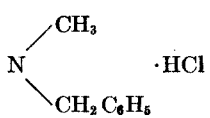
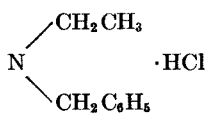
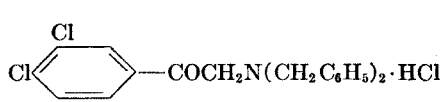
a	8416	N(*n*-butyl)$_2$	0.1	5R;3K	6[n]	1.5182–1.5188	174–176/2 mm.
b	6651	N(*n*-amyl)$_2$	0.1	5R;3K	12	$1.5122^{27°}$	159–161/1.5 mm.
c	10012	N(*n*-octyl)$_2$	0.2	7SR;3M	20	1.5048	239–240/4 mm.
d	8948		<0.1	7SR;3M	15	1.5807–1.5811	194–199/1–2 mm.

TABLE I *con't.*

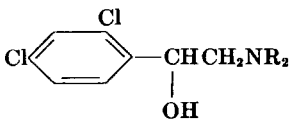
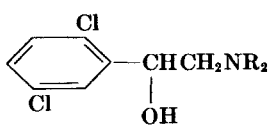
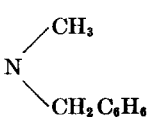
NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n_D^{20}[e]	B.P. OR M.P., °C.[f]
XXIII							
	8504		0.3	7SR;3M	6[n]	1.5172–1.5176	185–191/1 mm.
XXIV							
a	8928	N(*n*-butyl)$_2$·HCl	<0.08	11RQ[k]	—	acetone-ether[t]	101–102
b	15440[q]	N(*n*-octyl)$_2$	0.06	11R[k]	53[k]	1.5090	262–272/2 mm.
b_1	—	b-hydrochloride	—	—[k]	—	—[k]	210–212[v,x,u]
XXVA							
a	9516	N(ethyl)$_2$·HCl	0.2	5RQ;3HK	57	EtOH-ether	123
a_1	—	a-picrate	—	—	—	ethanol	153

b	6550	N(*n*-butyl)$_2$	0.3	5S;3K	12	1.5189–1.5200	—[y]
c	8417	N(*n*-amyl)$_2$	<0.6	5R;3K	34	1.5119	208–209/4 mm.
d	8505	N(*n*-octyl)$_2$	0.3 (1.5)[b2]	5R;3K	26	1.5061–1.5069[26°]	244–248/2 mm.
e	7982		0.3	6RQ;3L	24	EtOH-*i*PrOH	195–196[s]
f	8129	N($CH_2C_6H_5$)$_2$·HCl	0.06	8Q;3N	63[i]	CH_3OH	227–228
g	8503		0.15	5RQ;3K	54	isopropanol	134–136[s]
h	12306	NH-*n*-octyl·HCl	<0.15	11T[k]	56[r]	acetone	227–229 dec.
i	—	N(cyclohexyl)$_2$·HCl	—	11Q[k]	19[r]	3:7-acetone-ligroin	204–205

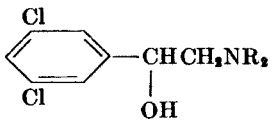
XXVB 

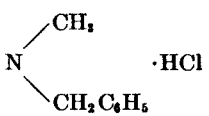
	—		—	3L	—	abs. ethanol	215–216

TABLE I *con't.*

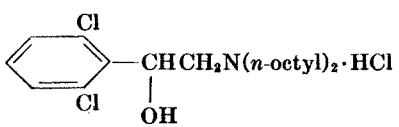
NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n_D^{20}[e]	B.P. OR M.P. °C[f]
XXVI							
a	9003	N(*n*-butyl)$_2$·HCl	0.6	11RQ	40[r]	acetone-ether	97.5–98.5[s]
b	15377[q]	N(*n*-octyl)$_2$·HCl	0.5 (2)[b1]	11Q	47[k,r]	ether	110–113
XXVII							
a	11639	N(*n*-octyl)$_2$·HCl	0.6 (3)[b2]	11Q	47.5[r]	EtOH-ether	96–98
b	8971		<0.06	11R	35.5[r]	1.5772[25°]	194–195/2 mm.

XXVIII



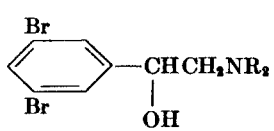
a	8957	N(*n*-butyl)$_2$·HCl	0.1+	5RQ;3K	14	acetone-ether	127–128[e]
b	8972		0.3	5RQ;3K	60	acetone-ether	176–177

XXIX



	8960		0.6	11Q	21[r]	abs. EtOH-ether	98–99.5

XXXA



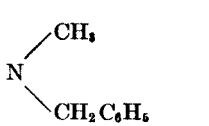
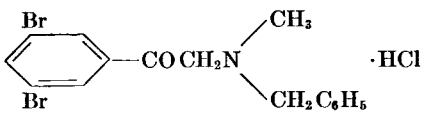
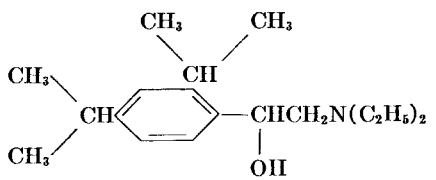
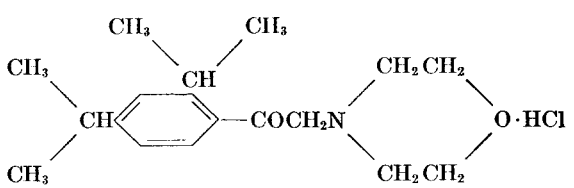
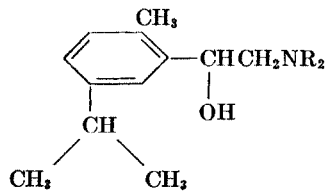
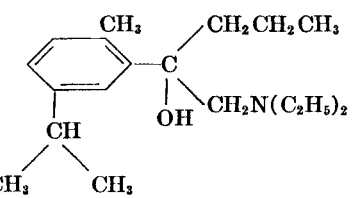
a	9037	N(ethyl)$_2$·HCl	0.2	6Q;3L	34[i]	abs. EtOH-ether	195–196
b	9902	N(*n*-amyl)$_2$·HCl	0.6	11SQ	32[r]	abs. EtOH-ether	127–128
c	9831		0.1	6SR;3L	39	1.6020	200–202/2 mm.

TABLE I *con't.*

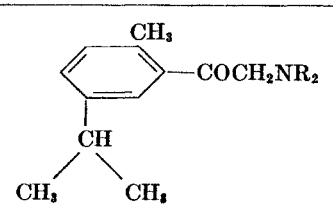
NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n_D^{20}[e]	B.P. OR M.P., °C[f]
XXXB							
	—		—	3L	86	abs. EtOH	198–201
XXXIA							
	3635		<0.1	5TR;3K	24[n]	$1.5000^{24°}$	135–137/2 mm.
XXXIB							
	3551		<0.06	3L	70[n]	ethyl acetate	218–220 dec.

XXXIIA



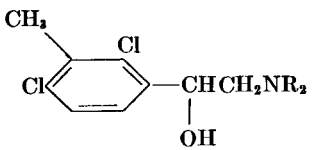
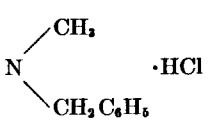
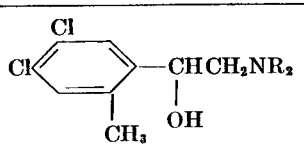
a	2598	N(ethyl)$_2$	<0.1	5R;3FK	32[n]	—	131/4 mm.
b	2630	N(*n*-butyl)$_2$·HCl	<0.15	5RQ;3FK	13[n]	acetone-ether	115–116
c	2597	piperidyl·HCl	<0.3	5Q[k]	34[i,n]	ethyl acetate	215.5–216
d	2599	morpholinyl·HCl	<0.06	5Q[k]	21[i,n]	ethyl acetate	178–179
e	6652		<0.06	—[k]	9[n]	1.5210[25°]	153/5 mm.

XXXIIB

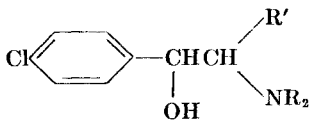


a	—	piperidyl·HCl	—	3FL	74[n]	EtOAc-EtOH	191–192
b	2600	morpholinyl·HCl	<0.03	3FL	69[n]	EtOAc-EtOH	208–209

TABLE I *cont'd*

NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n_D^{20}[e]	B.P. OR M.P., °C.[f]
XXXIII							
a	9832	N(*n*-butyl)$_2$	0.2	7R;3M	60	$1.5175^{23°}$	186–188/1 mm.
b	10011	N(*n*-amyl)$_2$	0.08	11R	40	$1.5257^{23°}$	204/1 mm.
c	12609	N(*n*-octyl)$_2$·HCl	(4)[b2]	11RQ	29	ethyl acetate	116
d	10220		0.04	11RQ	44	EtOH-ether	174
XXXIV							
a	11236	N(*n*-butyl)$_2$	0.6	11R	60	$1.5311^{16°}$	191–193/0.5 mm.
b	11237	N(*n*-amyl)$_2$	0.3	11R	51	$1.5266^{18°}$	202–203/0.5 mm.
c	11238	N(*n*-octyl)$_2$	0.6 (2[b1], 4[b2])	11R	76	$1.5151^{18°}$	245/0.5 mm.
c_1	—	c-hydrochloride	—	Q	—	EtOAc-pet. ether	126–128

XXXVA



(a–d) R′ = $-CH_3$; (e, f) R′ = $-CH_2CH_3$; (g–j) R′ = $-CH_2CH_2CH_2CH_3$

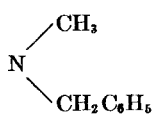
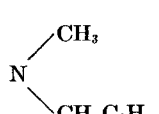
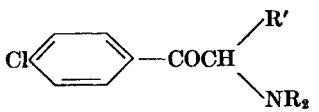
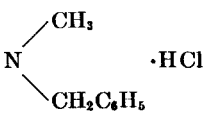
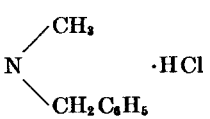
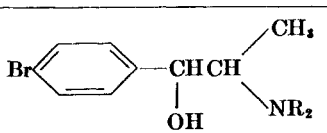
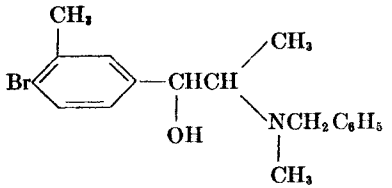
a	6750	N(*n*-amyl)$_2$	0.1	5TR;3K	25[n]	1.5001–1.5004	200–202/2 mm.
b	8400	N(*n*-octyl)$_2$	<0.03	5TR;3K	23[n]	1.4933–1.4936	206–210/1 mm.
c	6751		<1.0	6U;3L	—[i]	EtOH	91–92
d	6654	piperidyl·HCl	<0.15	6Q;3L	—[i]	abs. EtOH-ether	198–200
e	6425	N(*n*-butyl)$_2$	<0.06	5TR;3K	20[n]	$1.5040^{29°}$	136–139/1 mm.
f	6430	N(*n*-amyl)$_2$	<0.06	5TR;3K	30[n]	$1.5001^{27°}$	163.5–165/1.5 mm.
g	6424	N(*n*-butyl)$_2$	<0.03	5TR;3K	17[n]	$1.4998^{25°}$	155/1 mm.
h	7984		<0.03	6R;3L	22[i,n]	1.5522–1.5525	181–184/1.5 mm.
i	—	piperidyl	—	6R;3GL	38[i,n]	$1.5260^{25°}$	159/1 mm.
i_1	6655	i-hydrochloride	<0.06	Q	33[i,n]	abs. EtOH-ether	191.5–194.5[v]
j	10013	tetrahydroisoquinolyl·HCl	<0.03	6T;3G	—	acetone-ether	217–218 dec.[v]

TABLE I *cont'd*

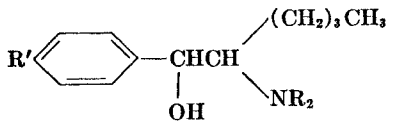
NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n_D^{20}	B.P. OR M.P., °C.[f]
XXXVB			(a–b_1) R′ = —CH_3; (c–e) R′ = *n*-butyl.				
a	8310		<0.06	3L	26[n]	abs. EtOH-ether	196–197
b	—	piperidyl	—	3N	54[n]	EtOH	64–65
b_1	6647	b-hydrochloride	<0.15	3P	47[n]	abs. EtOH-ether	210–213
c	—		—	3L	45[n]	ethyl acetate	158–160.5
d	6646	piperidyl·HCl	<0.15	3GL	47[n]	ethyl acetate	202–203 dec.
e	7400	tetrahydroisoquinolyl·HCl	<0.03	3G	76[n]	butanone	202.5–206[e]
XXXVI							
a	5045	N(*n*-butyl)$_2$	<0.1	5R;3K	—	1.5230	160–165/0.5 mm.[u]
b	6657	N(*n*-amyl)$_2$	0.1+	5TR;3K	37	$1.5095^{27°}$	163.5/1.5 mm.

XXXVII



	9586		<0.1	6U;3L	7[n]	ethanol	103–104

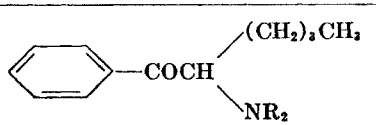
XXXVIIIA



(a–c) R′ = —H; (d) R′ = —CH_2CH_3; (f) R′ = —$C(CH_3)_3$(e) R′ = —$CH(CH_3)_2$;

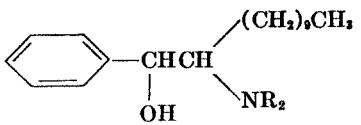
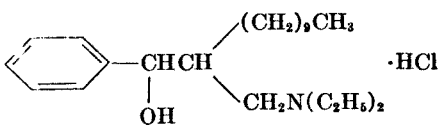
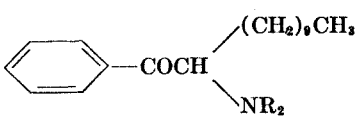
a	3102	N(*n*-butyl)$_2$	<0.6	5R;3K	16[n]	1.4918–1.4920	185–186/4 mm.
b	3096	piperidyl	<0.06	5R;3K	28[n]	1.5219[25°]	182/5 mm.
c	2740	morpholinyl·HCl	<0.15	5Q;3K	64[k]	CH_3OH-ether	215–217
d	3251	N(*n*-butyl)$_2$	<0.03	5TR;3K	19[n]	1.4830–1.4836[25°]	140–150/1–2 mm.
e	3547	N(ethyl)$_2$	<0.06	5TR;3K	—	1.4992[22°]	174–175/2 mm.[s]
f	3297	N(ethyl)$_2$·HCl	<0.15	5RQ;3K	24[n]	ethyl acetate	131–134

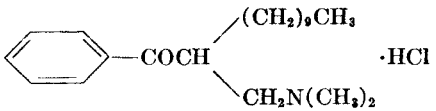
XXXVIIIB



a	2742	piperidyl·HCl	0.06	3L	15[n]	acetone	137–138
b	2741	morpholinyl·HCl	<0.06	3L	84[n]	acetone	191–194

TABLE I *concluded*

NO.	SN[a]	TYPE FORMULA —NR_2	Q[b]	PREP. METHOD[c]	YIELD (%)[d]	CRYST. FROM OR n_D^{20c}	B.P. OR M.P., °C.[f]
XXXIXA							
a	2013	N(ethyl)$_2$·HCl	<0.06	5Q;3K	46	acetone-ether	81–83
b	2612	piperidyl·HCl	<0.06	5Q;3K	—[k]	acetone	183–184
c	2625	morpholinyl·HCl	<0.06	5Q;3K	—[k]	acetone	178–180
XXXIXB							
	2748		<0.15	5Q[k]	8[n]	acetone	154–155
XXXIXC							
a	1628	piperidyl·HCl	<0.06	3L	67	acetone-ether	122–125
b	2626	morpholinyl·HCl	<0.02	3L	—	acetone	162–165

XXXIXD 

	—		—	—[k]	43[n]	acetone-ether	129–129.5

[a] The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned are tabulated in the Monograph (6).

[b] The symbol Q stands for quinine equivalent. The activities (6) listed in this table, except those in parentheses and otherwise specified by footnote, are against *P. gallinaceum* in the chick; most of them were determined at the National Institute of Health under the direction of Dr. G. Robert Coatney; a few were determined by Drs. L. T. Coggeshall and A. J. Porter at the University of Michigan (B-4), and by Drs. W. H. and L. G. Taliaferro and F. Coulston at the University of Chicago. [b1] These were the D-1 or G-5 tests against *P. lophurae* in the duck and were carried out at the Johns Hopkins Medical School under the direction of Dr. E. K. Marshall, Jr., and at the Squibb Institute for Medical Research under the direction of Dr. A. P. Richardson. [b2] Tests against *P. cathemerium* (G-4). [b3] These compounds were "slightly active" (*cf.* Ref. 6).

[c] This refers to the preparative method. The numbers and letters refer to the general "Procedures" and "Notes" given in the introduction.

[d] The yields are based on the α-bromo ketone unless otherwise specified. The yield is of good material though not usually fully purified.

[e] Refractive indices were taken at 20° unless otherwise specified in the body of the table.

[f] All melting and boiling points are corrected for exposed stem.

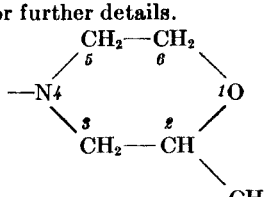
[g] Obtained as an oil which solidified on standing.

[h] As oil (b.p. 213–215°/2 mm.), n_D^{20} 1.5513.

[i] The yields based on the amino ketone hydrochlorides are: IAc = 33%; IIIB = 10%; IVa = 83%; b = 87%; c = 91%; g=91%; h = 87%; XVIAc=74%; XXAc = 90%; XXVAf = 80% (based on free base); XXXAa = 80%; XXXIIAc = 46%; d = 31%; XXXVAc = 52%; d = 52%; h =49%; i = 81%; i_1 = 70%.

[j] *i*PrOH = isopropanol.

[k] See experiment section for further details.

[m] 2-Methylmorpholinyl = 

[n] The yield is based on the parent acetophenone or the corresponding alkyl phenyl ketone.
[p] Prepared in ice-cold absolute ether by passing in dimethylamine and standing overnight.
[q] Drug Repository Number. These compounds were submitted for testing too late to be included in the Survey Monograph (6).
[r] Yield based on the bromohydrin.
[s] B.p. (of the free base): IIAp, 155°/2 mm.; s, 173–174°/1 mm.; u, 235–236°/4 mm.; XIa, 150–151°/2 mm.; c, 174–177°/2 mm.; XXVAe, 229–233°/1 mm.; g, 222–227°/1 mm.; XXVIa, 166–167°/1 mm.; XXVIIIa, 194–195°/3 mm.; XXXVIIIAe, 202–203°/15 mm.
[t] Crystallized from an acetone-ether-petroleum ether mixture.
[u] Not analyzed.
[v] These melting points were determined *in vacuo*.
[w] The sample decomposed on standing.
[x] Hygroscopic.
[y] Evaporated *in vacuo* at 206°.

constitute the chemical support for the results of the screening tests which have been published separately (6).

Two of the drugs described, namely, α-4-chlorophenyl-β-dioctylaminoethanol (IIAh) and α-4-chlorophenyl-β-N-tetrahydroisoquinolylethanol (IIAgg), were made by both of the above-outlined synthetic paths. The preparation of the former of these two compounds (IIAh) through the bromohydrin was considerably better than through the amino ketone (51% when calculated from the bromomethyl ketone). The expected and presumed mode of fission of the intermediate ethylene oxides involved[5] in the latter path through the bromohydrin was shown in both of the two cases to be as indicated above by the preparations also *via* the unequivocal path through the amino ketones, and by identification in each case of the two samples produced by the two different methods.

It is of interest to note that a successful practical short cut in the synthesis of the α-4-chlorophenyl-β-dioctylaminoethanol (IIAh) from the bromomethyl ketone was tried out in order to combine all of the steps into one operation, as follows: the *p*-chlorophenacyl bromide was added slowly to a refluxing solution of aluminum isopropoxide and excess dioctylamine and the reaction was completed in the usual way; upon working up the product the finished drug was isolated from the resulting mixture in 32% yield. This procedure was applied also in the case of α-(4-chloro-3-methylphenyl)-β-diamylaminoethanol (XVIAa) (yield 36%).

During the vacuum distillation of a number of ortho- and para-halogenophenyl amino alcohols of higher molecular weight (but not the meta-analogs) there were obtained crystalline by-products which were found in each case to consist of the hydrohalide of the secondary amine used in the preparation of the amino alcohol. This phenomenon was doubtless due to slow hydramine fission during the long heating involved, with production of the secondary amine and the halogenophenyl methyl ketone in which the nuclear halogen would be relatively more active than it was in the amino alcohol; this fission would be followed by interaction of the halogenophenyl methyl ketone with the secondary amine (or unchanged amino alcohol), with displacement of the now more active nuclear halogen, and with consequent formation and precipitation of a certain amount of the secondary amine hydrohalide. The significant activity of halogen ortho or para to an acetyl group has been reported under somewhat different but nevertheless analogous circumstances, for example, in the case of 2-bromo-4-methylacetophenone (11). To test this analogy and its bearing on the problem, dioctylamine and pure *p*-bromoacetophenone were heated together under conditions approximating those prevailing in the vacuum distillations of some of the amino alcohols, and the formation of significant amounts of dioctylamine hydrobromide was demonstrated.

This observed displacement of ortho and para halogen does not appear to be related to the reductive displacement which as been noted in the catalytic reduction of α-diethylamino-4-bromoacetophenone (12) to the amino alcohol. In the present cases, the aluminum isopropoxide used as the reducing agent would

[5] *Cf.* reference 10 and discussion, p. 1825.

not be expected to have any such effect. Furthermore, in some instances the formation of the secondary amine hydrohalide was actually seen to occur *after* the reduction step and *during* the purification procedure involving the distillation of the free amino alcohols; also hydramine fission during distillation of certain other amino alcohols where no halide ion was produced, was observed in later experiments, notably in the case of α-(4-chlorophenyl)-β-ditridecylaminoethanol (IIAn) where the free secondary amine was isolated in small amounts and identified.

EXPERIMENTAL

The following are generalized versions of the experimental methods employed in making the finished drugs.

The Preparation of the α-Bromomethyl Ketones

Procedure 1. The equivalent amount of bromine was added slowly under stirring and cooling to a commercial absolute ether solution of the methyl ketone. The bromination usually proceeded rapidly at 10–20°.

In *Procedure 2* the methyl ketone was brominated the same way except that a larger volume of solvent was used in order to ensure complete solution of the product, and the α-bromomethyl ketone was not isolated. The reaction solution was washed with water to remove hydrogen bromide and was dried; and aliquot portions were used directly in the reaction with the amines.

The Preparation of the Amino Ketones[8]

Procedure 3. An ethereal solution of the α-bromomethyl ketone (which, in some cases had not been isolated and purified) was treated under stirring with the secondary amine[7] (2–2.5 equivalents unless otherwise specified). The mixture was allowed to stand for eight to forty-eight hours, or until no further precipitation of the secondary amine hydrobromide could be observed. The secondary amine hydrobromide was removed by filtration and the amount thus obtained served to indicate the extent to which the reaction had gone.

Procedure 4. In a few instances the amino ketone was obtained by reacting the α-bromomethyl ketone in ether with one equivalent of the dialkylamine in the presence of an excess of dilute sodium or potassium carbonate. The resulting heterogeneous mixture was shaken for twelve to forty-eight hours; the ether layer was separated, washed with water and dried over sodium sulfate.

Preparation of the Amino Alcohols by Aluminum Isopropoxide Reduction of the Amino Ketones

Procedure 5. The crude free base was dissolved in dry isopropanol, mixed with 3–6 equivalents of 3 *N* aluminum isopropoxide and the mixture was heated under partial reflux at such a rate as to permit the slow distillation of acetone from the top of either a modified Hahn[8] or helices-packed column for 1–48 hours (until significant amounts of acetone could no longer be detected in the distillate by means of 2,4-dinitrophenylhydrazine test solution). Isopropanol was removed under reduced pressure (warming) and the residue was digested with excess 6–10 *N* sodium hydroxide. The mixture was then diluted with water and extracted with ether, and the ether solution was washed with water and then with saturated salt solution and was dried over sodium sulfate.

Procedure 6 (reduction of the purified amino ketone hydrochloride which had been pre-

[8] *Cf.* Ref. 8, p. 196.

pared according to Note L), *Procedure 7* (reduction of the crude oily amino ketone hydrochloride prepared according to Note M), and *Procedure 8* (reduction of the pure free base prepared according to Note N), were carried out like Procedure 5.

Procedure 9. The use of anhydrous aluminum chloride in reduction. In several instances one-half to one mole of anhydrous aluminum chloride per mole of the amino ketone (free base) was added to the aluminum isopropoxide solution in order to supply halide ion in concentration comparable to or greater than that involved when the salts of the amino ketones were used. The actual reduction was carried out as in Procedure 5. In one case, namely, XIXa, comparative preparations were carried out on the free base, with and without added aluminum chloride; the use of the aluminum chloride greatly improved the yield.

Preparation of Amino Alcohols Through the α-(Bromomethyl)benzyl Alcohols

Procedure 10. The aluminum isopropoxide reduction of certain of the α-bromomethyl ketones (3, 8, 9, 10) was carried out according to Procedure 5 until acetone could no longer be detected in the distillate (the reaction time varied from four to forty-eight hours). The isopropanol was evaporated under reduced pressure and the residue was shaken with cold 6 *N* sulfuric acid.

Procedure 11. The condensation of the bromohydrins with amines was carried out by dissolving the bromohydrin and two equivalents of the secondary amine in xylene or toluene and heating under reflux. In each case, after the reaction appeared to be complete, the mixture was cooled and diluted with absolute ether, and the precipitated hydrobromide of the secondary amine was filtered. The filtrate was washed, first with alkali, then with water, and was dried over sodium sulfate. The solvent was removed by distillation and the residue was purified by one or more of the methods listed in the Notes Q-W.

Notes to Procedures 1 and 2. (A) If the α-bromomethyl ketone precipitated from the cooled reaction mixture, the product (almost colorless) was filtered, washed with water, air-dried, and if necessary recrystallized from a suitable solvent (usually ethanol).

If the product did not precipitate, the reaction solution was washed with water and with dilute sodium carbonate, dried over sodium sulfate and concentrated. The crude product was then obtained either (B) as an oil in which case it was purified by vacuum distillation, or (C) as a solid in which case it was usually recrystallized, or in a few cases (D) vacuum distilled and then when possible (E) recrystallized.

Notes to Procedures 3 and 4. When more than the theoretical amount of the amine was used in the reaction (two equivalents in Procedure 3 and one in Procedure 4) the excess was occasionally removed as follows:

(F) In the case of water-soluble amines the excess amine was removed by extraction with water or saturated sodium chloride solution, and the ether solution was dried over sodium sulfate.

(G) In several cases, after extraction of the amine with water, the amino ketone was extracted with dilute hydrochloric acid and reprecipitated with sodium hydroxide and again extracted into ether.

(H) When the excess of the amine was not removed by extraction, it was removed by evaporation under reduced pressure.

(J) In the case of water-insoluble amines usually only the calculated two equivalents of amine was used and any excess remaining was not removed until after the amino ketone had been reduced to the amino alcohol.

Finally in all cases, the ethereal solution of the amino ketone was evaporated under reduced pressure. The residue consisted of a yellow or brown oil or a crystalline solid. The oily amino ketones were treated in one of the following ways:

(K) Reduction directly to the amino alcohol (Procedure 5).

(L) Solution in a suitable solvent, usually ether, and conversion into a crystalline hydrochloride by acidifying the solution with ethereal hydrogen chloride. The resulting mixture was diluted with ether and the product was filtered, washed with ether, and dried.

This product was often pure enough for use in the next step, or was further purified by recrystallization before reduction.

(M) Solution in a suitable solvent and conversion to an *oily* hydrochloride as in (L). The solvent was decanted; the residual oil was washed with ether by decantation, and without further purification was reduced to the amino alcohol.

The crystalline amino ketone (free base) was purified by (N) recrystallization or (P) conversion to and recrystallization of the hydrochloride.

Notes to Procedures 5–9. The partial decomposition of the higher-boiling amino alcohols during distillation was doubtless responsible for the low yields obtained in many cases in this investigation. Satisfactory results were usually obtained whenever such experiments were repeated under more favorable conditions for the distillation, involving such factors as better vacua, exclusion of oxygen by the use of an atmosphere of nitrogen, heating of the fractionating column, and in some cases resort to evaporation under low pressures onto a cold-finger drip-condenser under conditions approximating those in a molecular distillation.

(Q) The amino alcohol was precipitated from the ether solution as the hydrochloride by the addition of ethereal hydrogen chloride; it was then purified by crystallization, usually by dissolving in absolute ethanol and adding anhydrous ether.

If the crude free base did not readily form a crystalline hydrochloride it was (R) fractionally distilled under reduced pressure or (S) molecularly distilled and then fractionally distilled under reduced pressure and ordinary conditions. In the case of several of the amino alcohols of high molecular weight it was necessary to use a combination of (R) and (S) to effect purification.

(T) In several cases the ether extract containing the crude amino alcohol was extracted with 1–2 *N* hydrochloric acid to remove the basic material. Except for the few cases where the salt separated at this point, the acid layer was then neutralized with sodium hydroxide solution and the free base was extracted into ether. The amino alcohol was isolated according to one of the above methods.

In a few cases the amino alcohol separated as a solid after digestion of the residue with sodium hydroxide solution, and was filtered, washed with water and purified by (U) crystallization or (W) conversion into the hydrochloride followed by crystallization.

Notes to Procedure 10. (Y) In most instances the product separated as a solid and could be purified by crystallization from ligroin or 80% ethanol. (Z) In other instances the product was extracted into ether; the ether extract was washed with water, dried over sodium sulfate or potassium carbonate, and evaporated under reduced pressure; and the residue was fractionated under reduced pressure.

I. THE α-PHENYL-β-DIALKYLAMINOETHANOLS

These amino alcohols were prepared by condensation of phenacyl bromide with the appropriate secondary amine followed by aluminum isopropoxide reduction of the amino ketone to the amino alcohol. The few compounds of this type reported in the literature include the dimethyl (14, 15) and dibutylamino (16) compounds; the latter was made by the above method and reported since the present work was completed.

EXPERIMENTAL[6]

The preparation of α-dibenzylaminoacetophenone (IB) was carried out by the method of Busch and Hefele (13), in slightly improved yield (71%); m.p. 80–82° (B. and H., 81°); it decomposed on long standing.

α-Phenyl-β-dibenzylaminoethanol hydrochloride (IAf) (See Procedure 8UW.) A mix-

[6] All melting points and boiling points given in this paper are "corrected".

ture of 16 g. of α-dibenzylaminoacetophenone and 200 ml. of 1.5 *N* aluminum isopropoxide was heated under reflux for four hours, when the distillate gave a negative test for acetone. The isopropanol was evaporated under reduced pressure, and the residue was hydrolyzed by adding 5 ml. of water and then 50 ml. of 50% sodium hydroxide. After shaking the resulting mixture for two hours the oil which separated was extracted into 300 ml. of ether, washed with water, recovered by evaporation of the solvent under reduced pressure, and dissolved in ethanol. As the ethanol slowly evaporated, the amino alcohol (free base) crystallized; m.p. 52–53°; it was converted to the hydrochloride from dry ether by acidifying with ethereal hydrogen chloride; 14.5 g. (65%, calculated from phenacyl bromide); m.p. 211°. One recrystallization from 1:1 absolute ethanol-isopropanol gave 12.5 g. melting at 213°.

II. THE α-4-CHLOROPHENYL-β-DIALKYLAMINOETHANOLS

With one exception, namely, α-4-chlorophenyl-β-N-(2-hexylpiperidyl)ethanol (IIA11), the amino alcohols reported in this section were prepared through the amino ketones by reduction with aluminum isopropoxide. Failure was experienced in those condensations with α-bromomethyl ketones which involved the use of amines carrying a branch chain in the α-position, namely, 2-hexylpiperidine, diisopropylamine, and dicyclohexylamine. This phenomenon was observed also in other series, for example, the 3,4-dichloro. The amine in each case appeared to have reacted with the bromomethyl ketone, as indicated by the amount of secondary amine hydrobromide obtained, but no amino alcohol was obtained on working up the reduction mixture. The reaction probably did not involve reductive fission of the amino ketone during the aluminum isopropoxide reduction. In fact it seems more likely that the amino ketone had not been formed at all, or only in very small amounts, as was shown in one case, namely, the reaction of dicyclohexylamine with *p*-chlorophenacyl bromide in ether; this reaction produced a quantitative yield of the secondary amine hydrobromide after seventy-five hours at room temperature, and addition of ethereal hydrogen chloride precipitated the rest of the unused secondary amine, together with 2 g. of a yellow nitrogen-free crystalline substance (m.p. 188–190°) which has not yet been identified. This failure of the branched-chained amines to react with the bromomethyl ketone may be due to steric factors; the basic character of the amine evidently promotes enolization and condensation.

It appeared that generally better yields of the amino alcohols were obtained when the hydrochlorides rather than the free bases were used in the reduction (*cf.* 12), although only one control experiment was carried out to show this. Also it appeared that the yields depended to a large extent on the purity of the materials used.

The hydrochlorides of the higher dialkylamino compounds from dioctylamino up are progressively more soluble in ether than in water and may be recrystallized from ether.

The alkylamino alcohols of low molecular weight could be distilled under reduced pressure. The diundecyl, didodecyl, and ditridecylamino alcohols, however, could not be vacuum distilled without decomposition and hydramine fission. No indication of displacement of the para-chlorine was observed in these particular cases, however. Several low-pressure vacuum evaporations

onto a cold-finger condenser were necessary to effect a purification and to minimize hydramine fission. In the case of the ditridecylamino compound, distillation of a pure sample which had been obtained by several previous vacuum evaporations gave a distillate containing large amounts of a solid which was isolated and identified as the secondary amine (base) by conversion into its hydrochloride.

A few of the amino alcohols in this series, namely, dioctyl and tetrahydroisoquinolyl, were made both through the amino ketones and through the bromohydrin, and, as mentioned above, the β-N-(2-hexylpiperidyl) compound (IIA11) could be made only through the bromohydrin.

In this series two amino ketones were made by the Mannich reaction on *p*-chloroacetophenone, namely, the di-*n*-amyl and benzylmethylamino compounds. Reduction of these as the hydrochlorides by aluminum isopropoxide gave very poor results due to reductive fission of the dialkylamino groups. In the case of the benzylmethylamino compound, the secondary amine produced by reductive fission was actually isolated in 57% yield and identified. Because of this effect no amino alcohols of the type desired were obtained in this series in sufficient quantity for screening tests.

EXPERIMENTAL[6]

α-Bromo-4-chloroacetophenone, prepared by Collet (17) by bromination in carbon disulfide or glacial acetic acid solution, was made in ether according to Procedure 1A in yields of 85%.

α-Bromomethyl-4-chlorobenzyl alcohol was prepared according to Procedure 10Z. A solution of 23.5 g. (0.1 mole) of α-bromo-4-chloroacetophenone in 350 ml. of 1.3 *N* aluminum isopropoxide was refluxed for thirty-two hours. During the reduction, the acetone was collected and the amount determined by titration (*cf.* 18); 75%. The isopropanol was removed under reduced pressure and the residue hydrolyzed with dilute sulfuric acid. The bromohydrin was extracted into ether, washed with dilute sulfuric acid, sodium chloride solution and water, and dried over sodium sulfate. In one experiment the ether was evaporated, and the residual oil vacuum distilled and crystallized from ligroin; in another experiment the crude product was crystallized directly from ligroin, 15 g. (64%), m.p. 61–62°.

Anal. Calc'd for $C_8H_8BrClNO$: C, 40.80; H, 3.42.
Found: C, 40.74; H, 3.99.

α-4-Chlorophenyl-β-di-n-octylaminoethanol (IIAh). (a) Preparation from the bromomethyl ketone according to Procedures 3K;5R resulted in a yield of 38% of the amino alcohol (calculated from the bromomethyl ketone). The hydrochloride prepared from ether may be crystallized from dioxane or acetone, or preferably from ethanol by adding water until the solution becomes turbid, adding seed crystals, and allowing the mixture to cool in the ice-bath for several hours. It melted at 86–87°.

(b) In the hope of discovering a satisfactory short cut to the above method of preparing this amino alcohol, the following experiment was performed. A hot isopropanol solution of one equivalent of α-bromo-4-chloroacetophenone was added over a period of forty-five minutes to a refluxing isopropanol solution of 1.5 molal equivalents of aluminum isopropoxide and 1.5 equivalents of dioctylamine.[7a, c] The reduction to, and isolation of, the amino alcohol was carried out in accordance with Procedure 5R; yield, 32%.

[7(a)] Quantities of certain of the primary and secondary amines used in this research were prepared or secured by the Columbia University group under the direction of Dr. R. C.

(c) The amino alcohol was also prepared from the bromohydrin according to Procedure 11R (0.034 mole of the bromohydrin and 0.0704 mole of dioctylamine in 30 ml. of xylene, refluxed for 17.5 hours); it distilled at 215–217° (2 mm.); yield, 10.7 g. (80% calculated from the bromohydrin, or 52% calculated from the bromomethyl ketone).

α-4-Chlorophenyl-β-N-tetrahydroisoquinolylethanol (IIAgg). The hydrochloride precipitated upon attempted extraction of the ether solution with hydrochloric acid; 10.5 g. (59%), m.p. 204–209°. After crystallization from 100 ml. of water it melted at 229–231° (vac.).

The mother liquor from the crystallization was made basic and the remaining free amino alcohol was extracted with ether and crystallized from petroleum ether; white plates; m.p. 90–91°.

This amino alcohol was prepared also according to Procedure 11Q. A solution of 2 g. of the bromohydrin and 4.5 g. (0.034 mole) of tetrahydroisoquinoline in 15 ml. of xylene was refluxed for thirteen hours. The mixture was diluted with ether and the precipitate of amine hydrobromide was filtered. Ethereal hydrogen chloride precipitated the hydrochloride, which was crystallized from 30 ml. of water; 1.82 g. (66%); m.p. 197–217°. The free base isolated from the filtrate melted at 91° after two crystallizations from petroleum ether. A mixture melting point with the base prepared by reduction of the amino ketone showed no depression.

α-4-Chlorophenyl-β-di-n-dodecylaminoethanol (IIAm) was purified by a series of fractional vacuum evaporations of material which had previously distilled at 239–262° (2 mm.), onto a cold-finger condenser at 144–162° (2 mm.).

α-4-Chlorophenyl-β-di-n-tridecylaminoethanol (IIAn) distilling at 231–281° (2 mm.) was freed from ditridecylamine[7a], by dissolving in ethyl acetate and adding ethereal hydrogen chloride to precipitate the secondary amine hydrochloride. Fractions were combined from several vacuum evaporations and distillations, and material so obtained was then fractionally evaporated at 2 mm. The fraction evaporating over a temperature range up to 150° contained large amounts of ditridecylamine which was isolated and identified. The fraction evaporating at 152–173° was analyzed.

β-Di-n-amylamino-4-chloropropiophenone hydrochloride (IICa). A mixture of 31 g. of 4-chloroacetophenone, 23 g. of diamylamine hydrobromide, 18 g. of paraformaldehyde, 75 ml. of absolute ethanol, and 2 ml. of ethanolic hydrogen chloride was refluxed for twenty-four hours and the solvent evaporated in a current of air. The residual oil was treated with dilute sodium hydroxide and extracted with ether, washed, dried, and recovered by evaporation of the solvent. It was converted into the hydrochloride by dissolving in acetone and acidifying (Congo Red) with ethereal hydrogen chloride; 24 g. (67%); m.p. 65–72°. Six crystallizations from acetone by adding dry ether gave a product of m.p. 100–103°.

Reduction by aluminum isopropoxide (Procedure 6) gave a product of low and wide boiling range which evidently contained a large amount of diamylamine formed through reductive fission.

β-Benzylmethylamino-4-chloropropiophenone hydrochloride (IICb); made like IICa in 63% yield (17 hours refluxing); recrystallized from ethanol; m.p. 170–172°.

In the aluminum isopropoxide reduction (Procedure 6) of IICb (refluxing for 9 hours) a crystalline salt was obtained in 57% yield from ether by ethereal hydrogen chloride; it was identified as benzylmethylamine hydrochloride.

III. THE α-4-BROMOPHENYL-β-DIALKYLAMINOETHANOLS

Seventeen new amino alcohols in this series were prepared through the reaction between the α-bromomethyl ketone and the appropriate amine followed by

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Elderfield. [b] Some of the amines were made under the direction of Dr. W. S. Cottle, at Rutgers University. [c] Several were supplied by the Sharples Co. [d] A number of the benzylalkylamines are new and are described in a separate paper (Ref. 90).

aluminum isopropoxide reduction of the amino ketone. Ten amino ketones were also isolated in this series, one of which, α-N-morpholino-4-bromoacetophenone, has been prepared previously (19). The preparation of lower members of this series was omitted because during the course of this investigation it was learned that they were being made in another laboratory (12).

The attempt to obtain homologs of typical amino alcohols led to the study of the Mannich reaction in this series. As in the case of the *p*-chloro analogs, the β-amino ketones could be obtained readily but reduction did not appear to be practical in the few preliminary trials. In one case, that of the dipropylamino compound (IIIB), reduction gave a small yield (10%) of the desired γ-amino alcohol.

EXPERIMENTAL[6]

α,4-Dibromoacetophenone (17, 20, 21) was prepared in the usual way in yields of 90% (Procedure 1A).

α-4-Bromophenyl-β-di-n-amylaminoethanol (IIIAb) (illustrating Procedures 5TR;4K). To a 200-ml. dry ether solution of 27.8 g. (0.1 mole) of α,4-dibromoacetophenone, cooled in an ice-bath, was added 17 g. (0.108 mole) of diamylamine. After the initial reaction had subsided, 140 ml. of 15% sodium carbonate was added, and the resulting mixture was shaken mechanically for two days. The ethereal solution was washed and dried over sodium sulfate; the solvent was evaporated under reduced pressure, and the residual oil was dissolved in dry isopropanol and 100 ml. of 3 *N* aluminum isopropoxide. The reduction required one day (refluxing). The isopropanol was evaporated under reduced pressure, and the dark residue was digested with 8 *N* sodium hydroxide. The reduction products were extracted into ether, and the ether layer was shaken with 6 *N* hydrochloric acid. Three layers formed. The ether layer containing the non-basic matter was discarded. The aqueous and oily layers were neutralized with 5 *N* sodium hydroxide solution, and the amino alcohol was extracted into ether; the ether layer was washed and dried over sodium sulfate with simultaneous Darco treatment. The product was isolated and distilled under reduced pressure; 33.1 g; b.p. 167–170° (2 mm.). A second treatment in ether solution with Darco and redistillation under reduced pressure gave 18.6 g. (52%).

α-4-Bromophenyl-β-di-n-octylaminoethanol (IIIAf) (illustrating Procedures 5TR,3K, and the loss of nuclear halogen). To a suspension of 27.8 g. (0.1 mole) of the α-bromomethyl ketone in 100 ml. of dry ether, was added under cooling and stirring 49 g. (0.2 mole) of dioctylamine. After the reaction mixture was allowed to stand at room temperature for eight hours, 24 g. (94%) of the secondary amine hydrobromide precipitated. The reduction was carried out as described above (for IIIAb). Fractionation under reduced pressure gave 6 g. (14%) of slightly yellow product.

One of the fractions contained large amounts of a solid mixed with the oily product. This fraction was diluted with dry ether and the mixture was filtered. Recrystallization of the solid from ethanol-ligroin gave a colorless product which was identified as dioctylamine hydrobromide by analysis (Calc'd for $C_{16}H_{35}N \cdot HBr$: N, 4.35. Found: N, 4.52), and by melting point and mixture melting point.

α-[4-(2-Ethylmorpholinyl)]-4-bromoacetophenone hydrochloride (IIICf) (illustrating Procedure 3GL). Thirty-two grams (0.28 mole) of 2-ethylmorpholine[7b] was added slowly with stirring to a suspension of 35 g. (0.13 mole) of the α-bromomethyl ketone in 350 ml. of dry ether. Filtration after three hours gave 24.4 g. (99%) of the secondary amine hydrobromide. The ether filtrate was extracted four times with 200-ml. portions of water, and then three times with 175-ml. portions of 1 *N* hydrochloric acid. The acid solutions were combined and neutralized with 5 *N* sodium hydroxide. The oil which separated was

extracted into 250 ml. of ether; the ether layer was separated, and the solvent was evaporated under reduced pressure. After the residual oil had been dried further under a good vacuum, it was dissolved in 300 ml. of absolute ether and neutralized (Congo Red) with ethereal hydrogen chloride. The ether was decanted from the amino ketone hydrochloride which precipitated. This crude product was digested with acetone; 37 g. (82%); m.p. 220–222° dec. Recrystallization from ethanol gave 26 g. of pure product melting at 228° dec. *in vacuo*.

α-4-Bromophenyl-β-[4-(2-ethylmorpholinyl)]ethanol hydrochloride (*IIIA1*) (illustrating Procedure 6TQ). Thirty grams of a suspension of 30 g. of the amino ketone hydrochloride in 250 ml. of 1.8 *N* aluminum isopropoxide was heated under reflux for 3.5 hours, when no more acetone was being produced. The isopropanol was distilled under reduced pressure. To the residue was added 5 ml. of water and then 70 ml. of 10 *N* sodium hydroxide. After one hour of shaking, the oil which separated was extracted into 300 ml. of ether; the ether layer was separated, washed well with water, and extracted twice with 200-ml. portions of 1 *N* hydrochloric acid. The combined acid solution was made alkaline (litmus) with 5 *N* sodium hydroxide, and the oil which separated was extracted by ether. The ether layer was separated, washed with water, dried over sodium sulfate, and neutralized with ethereal hydrogen chloride. The precipitated amino alcohol hydrochloride was recrystallized from a 9:1 isopropanol-methanol mixture; 19 g. (63%); m.p. 186–187°.

The reaction between 4-bromoacetophenone and di-n-octylamine. A mixture of 4 g. (0.02 mole) of the bromomethyl ketone and 9.6 g. (0.04 mole) of dioctylamine was heated at 235–245° for thirty minutes, conditions simulating those involved in the vacuum distillation of the amino alcohols. After the mixture had cooled, dry ether was added, and 0.5 g. of dioctylamine hydrobromide precipitated and was identified.

β-Di-n-propylamino-4-bromopiopuophenone hydrochloride (*IIIDa*) was made by refluxing for twenty-one hours a mixture of dipropylamine hydrochloride, *p*-bromoacetophenone, paraformaldehyde, and a small amount of concentrated hydrochloric acid with dioxane or absolute ethanol as solvent. The product was obtained as an oil and was separated from unreacted dipropylamine by fractional precipitation of the hydrochlorides with standard ethereal hydrogen chloride.

α-4-Bromophenyl-γ-di-n-propylaminopropanol hydrochloride (*IIIB*). One gram of IIIDa was added to 12 ml. of warm 2 *N* aluminum isopropoxide. After refluxing for twenty minutes and working up the product, and crystallizing it as the hydrochloride, 0.1 g. of pure material was obtained.

The *di-n-butylamino* compound (IIIDb) was made like IIIDa using absolute ethanol as solvent.

IV. THE 4-IODOPHENYL-α-DIALKYLAMINO KETONES AND ALCOHOLS

Seven amino alcohols and three amino ketones were made from 4-iodoacetophenone. Attempts to make the diisopropylamino compounds failed, evidently due to steric factors which interfered with the formation of the amino ketone.

EXPERIMENTAL

4-Iodoacetophenone. The preparation by the Friedel-Crafts reaction in carbon disulfide (22), reported as proceeding in 80–95% yields using acetyl chloride and resublimed anhydrous aluminum chloride, gave only poor yields in our hands using technical aluminum chloride. Large amounts of iodine were liberated during the reaction. This may have been caused by impurities in the aluminum chloride, for example, iron (*cf.* Ref. 23). The yields were brought to 76% by adding the iodobenzene slowly to the refluxing reaction mixture.

This product was brominated according to Kimura (22).

V. THE α-4-FLUOROPHENYL-β-DIALKYLAMINOETHANOLS

EXPERIMENTAL[6]

4-Fluoroacetophenone (24, *cf.* also Ref. 25) was prepared by slow dropwise addition of 100 g. of acetic anhydride into a well-stirred mixture of 112 g. of fluorobenzene, 465 g. of anhydrous aluminum chloride and 700 ml. of carbon disulfide, with subsequent refluxing for two hours; yield 100 g. (62%); b.p. 195°.

α-Bromo-4-fluoroacetophenone was prepared by dropwise addition of 61 g. of bromine into a stirred solution of 43 g. of 4-fluoroacetophenone in 200 ml. of absolute ether. After washing the solution and distilling, a fraction boiling between 140–150° (5 mm.) was collected (the bulk distilled at 148°); yield 70 g. (96%); it crystallized on standing; m.p. 48–49°.

Anal. Calc'd for C_8H_6BrFO: C, 44.27; H, 2.79.
Found: C, 44.52; H, 3.00.

α-4-Fluorophenyl-β-di-n-octylaminoethanol (*Va*). A mixture of 38 g. of dioctylamine, 21 g. of α-bromo-4-fluoroacetophenone, 125 ml. of ether, 25 g. of potassium carbonate, and 10 ml. of water was shaken for twenty-four hours; the ether solution was separated and evaporated, and the residual oil (46 g.) was added to 150 ml. of 3 *N* aluminum isopropoxide. After refluxing for two hours the solvent was evaporated on a water-bath at 50°. Hydrolysis with 3 *N* hydrochloric acid, treatment of the precipitated hydrochloride (an oil) with 10% sodium hydroxide and extraction with ether, gave the free base as an oil which distilled at 195–197° (1 mm.) (the major portion distilled at 196°); yield 26 g. (56%).

α-4-Fluorophenyl-β-(benzyl-n-butylamino)ethanol (*Vc*). The amino ketone (Procedure 3) formed quickly upon interaction of 21 g. of the α-bromo ketone and 52 g. of benzylbutylamine[7d] in 125 ml. of absolute ether (15 min.); crude yield 33 g. This product was reduced (Procedure 5) and the reaction complex was hydrolyzed with 50% potassium hydroxide. The oily product was dissolved in ether and treated with 6 *N* hydrochloric acid; the hydrochloride separated as a third layer, and was isolated and converted under ether to the base with 10% sodium hydroxide. The resulting oil distilled at 172–174° (1 mm.) and was redistilled; the major portion boiled at 173.5° (1 mm.); yield 22 g. (66%).

VI. THE α-3-CHLOROPHENYL-β-DIALKYLAMINOETHANOLS

3-Chloroacetophenone, first made by the decarboxylation of α-carbomethoxy-3-chloroacetophenone (26), has been obtained in quantity through *meta*-nitration of acetophenone (27), followed by reduction, diazotization and the Sandmeyer reaction. It had been observed (27) that the use of nitric acid alone in the nitration of acetophenone gives a mixture of isomeric acetophenones, whereas the nitric and sulfuric acid mixture gives chiefly the meta compound. It has usually been necessary to limit the size of the run because either an undue temperature rise, or the very slow addition of the nitrating mixture necessary to prevent the rise, has an adverse effect on the purity of the product (28). Addition of dry-ice directly to the reaction mixture is advantageous in the nitration of a substituted acetophenone (29), and dry-ice has been used more recently in the nitration of acetophenone itself (30, 12). It was found here that at temperatures below −30° the viscosity became too great for effective stirring. Excellent results were obtained at reaction temperatures of −20° to −15° in batches of six times the size formerly considered as the optimum (30).

EXPERIMENTAL

Preparation of 3-nitroacetophenone (*cf.* ref. 12, 29, 30). A 3-liter 3-necked flask charged with 900 ml. of concentrated sulfuric acid and equipped with a stainless steel stirrer was

mounted in an insulated 10-quart pail filled with ethanol to which dry-ice was added as needed (about 10 lbs. was required). Acetophenone (360 g., 3 moles) was added slowly, followed by the nitrating mixture consisting of 360 ml. of concentrated sulfuric acid and 240 ml. (3.9 moles) of nitric acid (precooled to 0°). The additions were made at such a rate that the heat evolved prevented the mixture from cooling to the point of freezing or becoming too viscous to stir; the actual mixture temperature ranged from −30° to −20° at the beginning of the nitration, and from −20° to −15° as the last of the nitrating mixture was added. The actual time required for adding the nitrating mixture was about forty-five minutes, and a few minutes later the mixture became extremely viscous; the cooling bath was then removed, and when the mixture had warmed sufficiently to flow, it was poured with stirring into 13.5 l. of ice and water. The cream-colored precipitate was washed repeatedly with water and once with ice-cold ethanol; it was pure enough for further use; yield 198 g. (81%).

Preparation of 3-chloroacetophenone. The directions used were practically identical with those in "Organic Syntheses" (31) for the preparation of 3-chlorobenzaldehyde; the yield was 68%. It was *brominated* according to Procedure 1, using carbon tetrachloride as a solvent.

VII. THE α-2-CHLOROPHENYL-β-DIALKYLAMINOETHANOLS

EXPERIMENTAL[6]

α-Bromo-2-chloroacetophenone. An ether solution of 87.5 g. (0.5 mole) of *o*-chlorobenzoyl chloride (32) was added dropwise with stirring to a cold solution of 1.5 moles of diazomethane in 2.5 l. of ether, and the mixture was allowed to stand overnight. Treatment with 215 ml. of 40% hydrobromic acid in an equal volume of ether (effervescence), washing the ether layer with water and sodium bicarbonate solution, drying over sodium sulfate and distilling off the ether, gave an oil which was vacuum distilled [92 g. (79%); b.p. 129–131° (4.5 mm.)] and redistilled; b.p. 97.5–98° (1 mm.); n_D^{20} 1.5903.

Anal. Calc'd for C_8H_6BrClO: C, 41.15; H, 2.59.
Found: C, 41.33; H, 2.75.

VIII. THE α-3-BROMOPHENYL-β-DIALKYLAMINOETHANOLS

The route for the preparation of 3-bromoacetophenone, needed for this series, was the reduction of 3-nitroacetophenone (see section VI), followed by diazotization and treatment with cuprous bromide.

EXPERIMENTAL[6]

Preparation of 3-bromoacetophenone followed approximately the old procedure (33) starting with 3-nitroacetophenone, reducing this with stannous bromide (*cf.* 34), diazotizing the 3-aminoacetophenone in dilute hydrobromic acid and treatment with cuprous bromide. Light yellow oil, *b.p.* 102–106° (4 mm.); yield 63%.

Bromination was carried out according to Procedure 1DE; b.p. 154–159° (10 mm.); m.p. 48°; recrystallized from ligroin, m.p. 51° (E., G., and J., 51°).

IX. α-2-BROMOPHENYL-β-BENZYLMETHYLAMINOETHANOL

2-Bromoacetophenone, the starting material, [first prepared through nitration of acetophenone, separation of the ortho and meta nitro derivatives, reduction and diazotization (35, 36)] has been made more conveniently from 2-bromobenzoic acid through the acid chloride, the amide, and the nitrile [by addition of methylmagnesium iodide (37) to the latter]. An effort was made to obtain 2-bromoacetophenone directly by methylation of the 2-bromobenzoyl chloride with dimethylcadmium, following the successful work of Gilman and Nelson (39)

on benzoyl chloride; however no reaction took place, presumably because of the ortho-bromine. Alkylation with methylmagnesium iodide gave a mixture of products which was not further investigated.

EXPERIMENTAL[6]

2-Bromobenzoyl chloride (38) was made in 95% yield from 2-bromobenzoic acid (Eastman) by means of thionyl chloride (refluxing for twenty-two hours); b.p. 120–126° (15 mm.); n_D^{20} 1.5965. When added to a large excess (twelve equivalents) of cold concentrated ammonium hydroxide it gave *2-bromobenzamide* in 97.6% yield; m.p. 159.5–161.5° [S. (38), 155–156°]. Refluxing with three equivalents of thionyl chloride for seventeen hours followed by steam distillation gave *2-bromobenzonitrile* in 84% yield; m.p. 52.5–54.5° [S. (40), 51°]. This nitrile reacted with three equivalents of methylmagnesium bromide to give *2-bromoacetophenone*, (69%), b.p. 131–135° (20 mm.) [B. and S. (37), 118–120° (16 mm.)]; n_D^{20} 1.5667–1.5678; semicarbazone, m.p. 175–177° [E., G., and J. (33), 177°].

α,2-Dibromoacetophenone was prepared in 73% yield by Procedure 1B; b.p. 104–127° (1.8 mm.), n_D^{20} 1.6040–1.6126.

Anal. Calc'd for $C_8H_6Br_2O$: C, 34.57; H, 2.18.
Found: C, 34.04; H, 2.16.

X. α-3-IODOPHENYL-β-DIALKYLAMINOETHANOLS

The 3-iodoacetophenone was made from 3-nitroacetophenone through the 3-amino derivative by diazotization (*cf.* section VI).

EXPERIMENTAL[6]

3-Iodoacetophenone (41) was obtained in 57% yield from 3-nitroacetophenone as follows: 109 g. (0.68 mole) of 3-nitroacetophenone was added in one portion (stirring) to 450 g. of stannous chloride dihydrate and 600 ml. of concentrated hydrochloric acid at 3–5°. The temperature was allowed to rise slowly and was maintained at 80–90° to complete the reduction. Cooling to 2–5° gave a pasty suspension to which about 300 ml. of water was added. A solution of 45 g. (0.66 mole) of sodium nitrite in 85 ml. of water was added slowly, delivered below the surface through a capillary, until a positive reaction in the starch-iodide test was obtained; the mixture was allowed to stand for fifteen minutes, and was treated with aqueous urea to destroy the excess nitrous acid. A solution of 2.9 g. (1.32 moles) of potassium iodide was added slowly; the mixture was allowed to warm to room temperature overnight, and then was heated on the water-bath until evolution of nitrogen ceased. The dark oil which separated was washed and distilled; 92 g. (57%), b.p. 102° (2 mm.) [E., M., and W. (41), 128.5° (8 mm.)]

α-Bromo-3-iodoacetophenone. (See Procedure 1A). Yield 75%. Recrystallized from methanol; m.p. 62–65°.

Anal. Calc'd for C_8H_6BrIO: C, 29.57; H, 1.86.
Found: C, 29.31; H, 2.07.

XI. THE α-2-IODOPHENYL-β-DIALKYLAMINOETHANOLS

The commercially available 2-iodobenzoyl chloride was used as the starting material rather than 2-aminoacetophenone (42). The α-bromomethyl ketone was obtained *via* the efficient path through the acid chloride and diazo ketone in an over-all yield of 70%.

EXPERIMENTAL[6]

α-Bromo-2-iodoacetophenone. A solution of 133.5 g. (0.5 mole) of 2-iodobenzoyl chloride in twice its volume of absolute ether was added slowly to 1.4 moles of diazomethane in

2 l. of ether which had previously been dried over potassium hydroxide (effervescence). After standing overnight, 219 ml. of 48% hydrobromic acid in an equal volume of ether was added; frothing occurred and an aqueous layer separated. After standing for two hours, the ether layer was separated, washed, dried, and concentrated. The resulting oil was vacuum distilled; 114 g. (70%), b.p. 140–143° (2 mm.). It was redistilled; b.p. 162–164° (6 mm.).

Anal. Calc'd for C_8H_6BrIO: C, 29.57; H, 1.86.
Found: C, 29.72; H, 1.90.

α-2-Iodophenyl-β-benzylmethylaminoethanol (*XId*), prepared according to Procedure 7SQ, was vacuum distilled; b.p. 197–200° (2 mm.) (55%). Evidence was observed of hydramine fission upon distillation and some benzylmethylamine hydriodide was obtained. Redistillation produced more of the fission products. Evaporating onto a cold-finger condenser at 95–100° (0.5 mm.) gave a sample which contained negligible amounts of fission products, as shown by failure to obtain a precipitate of more of the salt on dilution with ether.

XII. THE α-4-ALKOXYPHENYL-β-DIALKYLAMINOETHANOLS

The new *p*-butoxyacetophenone used as a starting material was prepared by a Friedel-Crafts reaction on butyl phenyl ether. The low yield (45%) may in part be explained by the formation of the by-product, 1,1-di-(*p*-butoxyphenyl)-ethylene, $(p\text{-}C_4H_9OC_6H_4)_2C=CH_2$, a considerable amount of which was isolated from the reaction mixture. This type of compound has been reported by Gattermann and co-workers (43, 44) in the preparation of *p*-methoxyacetophenone, and by Skraup and Nieten in the preparation of *p*-methoxybutyrophenone (45).

Bromination of the methyl ketones proceeded readily in ether and the resulting solutions were used without isolation of the bromomethyl ketones in the condensations with the amines.

EXPERIMENTAL[6]

α-Bromo-4-methoxyacetophenone had been prepared previously by bromination of 4-methoxyacetophenone in glacial acetic acid (46). In this investigation ether was used as the solvent according to Procedure 1. After crystallization from ethanol it melted at 69–71° (B. (46), 70–71°).

α-4-Methoxyphenyl-β-di-n-amylaminoethanol (*XIIa*). The crude amino alcohol was first evaporated *in vacuo* at 130–154° (3 mm.) and then purified according to Notes TS.

α-Bromo-4-ethoxyacetophenone was prepared according to Procedure 2 (not isolated).

4-Butoxyacetophenone. A mixture of 214 g. (1.43 moles) of butyl phenyl ether (47), 186 g. (2.37 moles) of acetyl chloride and one liter of dry carbon disulfide was cooled in an ice-bath and 230 g. (1.72 moles) of powdered anhydrous aluminum chloride was added gradually with stirring over a period of fifteen minutes. The ice-bath was removed and the mixture was stirred at room temperature for 7.5 hours and hydrolyzed with ice and hydrochloric acid. The carbon disulfide layer (the aqueous layer was extracted once with more carbon disulfide) was extracted six times with 6 *N* hydrochloric acid, washed with water, and dried over calcium chloride. The solvent was removed under reduced pressure and the crude residual ketone was vacuum distilled. The fraction boiling at 125–155° under 2 mm. pressure (yield 126 g.) was refractionated; b.p. 127–131° at 3 mm.; 120 g. (44%); n_D^{23} 1.5281–1.5290.

The *oxime* prepared in the usual way melted at 86° after repeated crystallization from 60–80% ethanol.

Anal. Calc'd for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27.
Found: C, 69.21; H, 8.34.

1,1-Di-(4-butoxyphenyl)ethylene. The residue remaining in the flask after the first distillation of the crude 4-butoxyacetophenone was crystallized from ethanol after Norit treatment; white plates; m.p. 125–126°; yield 34.2 g. (15%). A sample after four crystallizations from ethanol melted at 127°.

Anal. Calc'd for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70.
Found: C, 81.77; H, 8.83.

α-Bromo-4-butoxyacetophenone was prepared according to Procedure 2 (not isolated).

XIII. THE α-4-ALKYLPHENYL-β-DIALKYLAMINOETHANOLS

Bromination of the methyl ketones, namely 4-*n*-hexyl-, 4-*n*-decyl-, and 4-*n*-dodecyl-acetophenones, proceeded easily in ether solution; the bromomethyl ketones were not isolated before condensation with the amines; and aluminum isopropoxide reduction of the crude amino ketones (also not isolated) proceeded without complications, except in the case of α-4-dodecylphenyl-β-diethylaminoethanol, where hydramine fission apparently interfered to some extent in the purification of the product by distillation under reduced pressure. The failure of dicylohexylamine to react with 4-isopropylphenacyl bromide in the usual way was also noted.

EXPERIMENTAL[6]

The 4-n-hexyl, 4-n-decyl, and 4-n-dodecylacetophenones were supplied by the OSRD group at Columbia University under Dr. Elderfield.

4-Cyclohexylacetophenone was prepared from phenylcyclohexane by the method of Mayes and Turner (48). It was found that fractional distillation of the crude ketone under reduced pressure gave a purer product than that obtained on crystallization. The 4-cyclohexylacetophenone used boiled at 165–173° (10 mm).

α-4-Hexylphenyl-β-di-n-amylaminoethanol (*XIIIc*) was first distilled at 4 mm. The fraction distilling at 155–225° was fractionated at 2 mm. The fraction distilling at 206–216° was then fractionally evaporated onto a cold-finger condenser under reduced pressure.

α-4-n-Decylphenyl-β-di-n-butylaminoethanol (*XIIIg*) was vacuum evaporated at 133–155° (2 mm.), redistilled (233–242°, 3 mm.), and then again vacuum evaporated.

α-4-n-Dodecylphenyl-β-diethylaminoethanol (*XIIIh*) was subjected to two vacuum distillations and one vacuum evaporation without obtaining an analytically pure sample. Since nitrogen analysis of the product was low, hydramine fission was suspected to have occurred to some extent.

XIV. α-4-BENZYLPHENYL-β-DI-*n*-BUTYLAMINOETHANOL

The procedure for the preparation of the starting material, 4-acetyldiphenylmethane (49), was modified somewhat to achieve the best results, and involved the slow addition of a mixture of approximately equimolar quantities of diphenylmethane and acetyl chloride to a mechanically stirred mixture of aluminum chloride and carbon disulfide. 4,4′-Diacetyldiphenylmethane (49) was also isolated as a by-product.

EXPERIMENTAL[6]

Preparation of 4-acetyldiphenylmethane and 4,4′-diacetyldiphenylmethane (49). A mixture of 168 g. (1.0 mole) of diphenylmethane and 80 g. (1.02 moles) of acetyl chloride was added dropwise to a mechanically stirred mixture of 175 g. (1.32 moles) of anhydrous aluminum chloride in 300 ml. of dry carbon disulfide at 0°. Upon completion of the addition

the reaction mixture was allowed to warm to room temperature, and was poured into a mixture of 3 l. of ice and 50 ml. of concentrated hydrochloric acid. The products were extracted with carbon disulfide and fractionated under reduced pressure. The first fraction, boiling up to 135° (3.5 mm.), consisted largely of diphenylmethane; 73 g.; the second fraction was crude 4-acetyldiphenylmethane; b.p. 135–190° (2–2.5 mm.); 41 g. (34% allowing for the recovery of diphenylmethane). A pure sample was obtained from material boiling at 162–184.5° (5 mm.) by recrystallizing from ethanol; m.p. 38–39° (D., 39°). The 4,4′-diacetyldiphenylmethane was isolated by recrystallizing the material boiling at 240–245° (6 mm.) from ethanol; m.p. 92.5–93° (D., 93°).

When acetyl chloride (1 mole) was added slowly to a mixture of diphenylmethane (1.5 moles), anhydrous aluminum chloride (1.5 moles) and carbon disulfide at 0°, only a 25% yield of the crude 4-acetyldiphenylmethane was obtained, together with small amounts of acetophenone (49) and 4,4′-diacetyldiphenylmethane.

4,4′-Bis(bromoacetyl)diphenylmethane was prepared according to Procedure 1A; yield 97%. Several recrystallizations from isopropanol and from butanone-ligroin gave a product of m.p. 137.5–138.5°.

Anal. Calc'd for $C_{17}H_{14}Br_2O_2$: C, 49.78; H, 3.44.
Found: C, 49.63; H, 3.95.

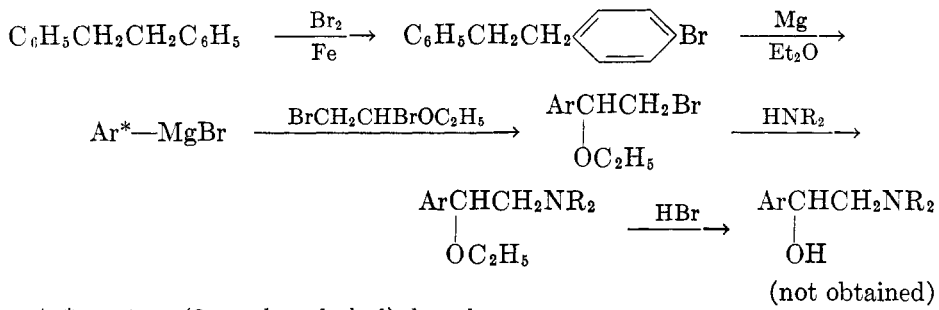
Attempted preparation of 4,4′-bis(2-di-n-butylamino-1-hydroxyethyl)diphenylmethane according to Procedure 3G and 5R resulted in considerable decomposition, and no tractable product was obtained.

4-(β-Diethylaminopropionyl)diphenylmethane hydrochloride (*XIVB*) was made by a typical Mannich reaction on 4-acetyldiphenylmethane (refluxing for 53 hours in ethanol) (see Sections II and III).

XV. α-4-(2-PHENYLETHYL)PHENYL-β-DI-*n*-BUTYLAMINOETHANOL

Two reaction paths were studied, one of these successfully. A representative amino alcohol in this series was prepared through 4-acetylbibenzyl which was obtained through the Friedel-Crafts reaction between bibenzyl and acetyl chloride in carbon disulfide. The 4-acetylbibenzyl was converted in the usual way, by α-bromination, condensation with dibutylamine, followed by aluminum isopropoxide reduction, into the amino alcohol.

An unsuccessful attempt was made to adopt the scheme followed by Späth and Göhring in the synthesis of ephedrine (50) as is illustrated in the following diagram; failure was experienced in the last step.

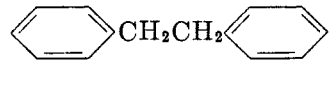


Ar* = 4 = (2 = phenylethyl)phenyl.

The Grignard reagent from bromobibenzyl was condensed with α,β-dibromoethyl ethyl ether (*cf.* Ref. 50) in 53% yield, and the resulting β-bromo ether was

condensed with diethylamine, giving an 82% yield of the pure dialkylaminoethyl derivative (as the hydrochloride). Repeated attempts to hydrolyze this ether to the desired amino alcohol according to the method of Späth and Göhring (50) resulted only in the formation of resinous products.

The α-(4-bibenzyl)-β-diethylaminoethyl ethyl ether hydrochloride was tested against avian malaria and was found to be inactive.

SN—2012  Q = < 0.3

EXPERIMENTAL[6]

4-Acetylbibenzyl. A suspension of 533 g. (4 moles) of aluminum chloride and 364 g. (2 moles) of bibenzyl in 750 ml. of dry carbon disulfide was vigorously stirred and cooled to 0°. Acetyl chloride (157 g., 2 moles) was added at such a rate as to maintain the temperature between 0–5°. The mixture was stirred overnight and poured onto ice and hydrochloric acid. The solid which was formed was filtered (54 g.); this was the diacetyl compound (see below). The carbon disulfide layer upon drying and concentrating gave a lower-melting solid which was crystallized from ethanol and fractionally distilled under a pressure of 3 mm. The fraction distilling at 172–173° weighed 277 g.; m.p. 68–70°. An analytical sample was prepared by three crystallizations from methanol.

Anal. Calc'd for $C_{16}H_{16}O$: C, 85.67; H, 7.19.
Found: C, 85.58; H, 6.89.

4,4'-Diacetylbibenzyl. The solid (54 g.) which was filtered from the carbon disulfide layer from the above experiment, was purified by repeated crystallizations from absolute ethanol; m.p. 167–168°.

Anal. Calc'd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81.
Found: C, 81.48; H, 6.62.

α-Bromomethyl-4-bibenzyl ketone was prepared by bromination of 4.5 g. of 4-acetylbibenzyl according to Procedure 1A. The product (3.6 g.) was crystallized several times from ligroin; m.p. 61°.

Anal. Calc'd for $C_{16}H_{15}BrO$: C, 63.38; H, 4.99.
Found: C, 63.80; H, 4.95.

α-4-(2-Phenylethyl)phenyl-β-di-n-butylaminoethanol hydrochloride (XVA). An aliquot portion (0.2 mole) of bromomethyl 4-bibenzyl ketone was reacted with 0.4 mole of di-*n*-butylamine according to Procedure 3F. Reduction to the amino alcohol was effected by Procedure 5Q using 200 ml. of 3 *N* aluminum isopropoxide under five hours of heating. Purification was difficult and six crystallizations from ethyl acetate and six from water were required to obtain an analytical sample.

4-Bromobibenzyl (51, 52). A mixture of 728 g. (4 moles) of bibenzyl and 8 g. of iron filings under a reflux condenser and under efficient stirring, was treated dropwise and without heating with 640 g. (4 moles) of bromine over a period of 1.5 hours. Hydrogen bromide was evolved briskly as the temperature rose. After the addition was completed, the dark red mixture was heated for three hours under stirring, and allowed to stand overnight; it was then stirred and treated with 350 ml. of 10% sodium hydroxide (30 min.), and washed with water. The resulting yellow oil was distilled; 444 g. (43%); b.p. 141–145° (3 mm.); 150 g. of unreacted bibenzyl was recovered from the lower-boiling portion of the distillate (118–120° at 3 mm.); and allowing for this recovery of starting material the yield of product was 63%, calculated from the bibenzyl consumed.

4-(β-Diethylamino-α-ethoxyethyl)bibenzyl hydrochloride. An ice-cold solution of bibenzylmagnesium bromide (prepared in the usual way from 0.1 mole of 4-bromobibenzyl) was treated slowly with 23.2 g. (0.1 mole) of α,β-dibromoethyl ethyl ether (53) and the mix-

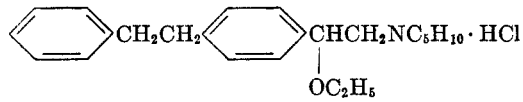
ture was stirred for twenty-two hours. The resulting dark brown mixture was poured onto ice (acidified). The ether layer was separated, and the water layer was extracted several times with ether. The combined ether extract was dried over sodium sulfate, concentrated, filtered from a small amount of solid, and evaporated; the residual oil was fractionally distilled. The fraction distilling at 183° (5 mm.) weighed 10 g. (31%).

On a much larger scale, using 540 ml. of 1.3 *N* bibenzylmagnesium bromide (0.71 mole) and 0.72 mole of α, β-dibromoethyl ethyl ether, and slowly adding the Grignard reagent to the dibromo ether and stirring for forty-eight hours at room temperature, a 53% yield of distilled product was obtained.

Fifty grams (0.15 mole) of this product was condensed with 43.7 g. (0.6 mole) of diethylamine by heating the mixture under reflux for eight hours and allowing it to stand at 50° for fifty-six hours. The diethylamine hydrobromide (11.2 g.; 72%) was filtered, and the ethereal filtrate was washed and dried. The hydrochloride of the product was precipitated by the addition of ethereal hydrogen chloride, and it was recrystallized from ethyl acetate; 45 g. (82%); m.p. 131–132°. The melting point after several recrystallizations was 132.5–133°.

Anal. Calc'd for $C_{22}H_{31}NO \cdot HCl$: C, 72.98; H, 8.91.
Found: C, 72.94; H, 8.87.

4-(β-Piperidyl-α-ethoxyethyl)bibenzyl hydrochloride.



A mixture of 10 g. (0.03 mole) of α-(4-bibenzyl)-β-bromoethyl ethyl ether and 5.2 g. (0.06 mole) of piperidine in 45 ml. of ether was heated under reflux for twenty-four hours, and was allowed to stand for twelve hours at room temperature. A 44% yield of piperidine hydrobromide was removed. The residue obtained upon evaporation of the ethereal filtrate was dissolved in acetone, and the hydrochloride was precipitated by addition of ethereal hydrogen chloride. Dilution with ether, cooling, and filtration produced 2.1 g. of product (19%); m.p. 167–170°. After several crystallizations from ethyl acetate it melted at 170–170.5°.

Anal. Calc'd for $C_{23}H_{31}NO \cdot HCl$: C, 73.88; H, 8.63.
Found: C, 73.98; H, 8.59.

XVI. THE α-(4-CHLORO-3-METHYLPHENYL)-β-DIALKYLAMINOETHANOLS

EXPERIMENTAL[6]

4-Chloro-3-methylacetophenone was prepared according to Noller and Adams (54) by the Friedel and Crafts acylation of ortho-chlorotoluene. *α-Bromo-4-chloro-3-methylacetophenone* was made from it by Procedure 1A, and was isolated and characterized, but the amino ketone and two amino alcohols were prepared directly from aliquot portions of ethereal solution of the crude α-bromomethyl ketone. The α-bromomethyl ketone was isolated in 69% yield by evaporating the reaction solvent and recrystallizing from ethanol; colorless rectangular rods; m.p. 56–57°.

Anal. Calc'd for C_9H_8BrClO: C, 43.67; H, 3.26.
Found: C, 43.51; H, 2.95.

α-(4-Chloro-3-methylphenyl)-β-di-n-amylaminoethanol (*XVIAa*) was prepared by the reaction between the bromomethyl ketone, diamylamine, and aluminum isopropoxide (in one operation) as described under IIAh(b).

α-(4-Chloro-3-methylphenyl)-β-di-n-octylaminoethanol (*XVIAb*). To an aliquot portion (0.1 mole) of the ethereal solution of the α-bromomethyl ketone was added 49 g. (0.2 mole) of dioctylamine. Procedures 3K and 5R were followed, with two vacuum distillations, and the product was obtained as a pale yellow oil.

α-Benzylmethylamino-4-chloro-3-methylacetophenone hydrochloride (*XVIB*). A mixture of an aliquot portion (0.3 mole) of the ethereal solution of the α-bromomethyl ketone and 72.8 g. (0.6 mole) of benzylmethylamine was worked up according to Procedure 3L. Repeated crystallizations gave the pure product as bundles of colorless needles.

α-(4-Chloro-3-methylphenyl)-β-benzylmethylaminoethanol hydrochloride (*XVIAc*). A mixture of 16.2 g. (0.05 mole) of the amino ketone hydrochloride, 200 ml. of dry isopropanol and 80 ml. of 3 *N* aluminum isopropoxide was treated according to Procedure 6Q. The amino alcohol hydrochloride was precipitated from dry ether by etheral hydrogen chloride and was recrystallized from absolute ethanol-ether as colorless needles.

XVII. THE α-(3-CHLORO-4-METHYLPHENYL)-β-DIALKYLAMINOETHANOLS

3-Chloro-4-methylacetophenone (*cf.* 55) needed for the preparation of these compounds, was made in a new way through nitration of 4-methylacetophenone, stannous chloride reduction, diazotization, and the Sandmeyer reaction.

EXPERIMENTAL[6]

Preparation of 4-methyl-3-nitroacetophenone followed the nitration procedure described in Section VI except that the reaction temperature was maintained just under −15° (*cf.* 56). The crude product was a very pale yellow solid; yield 94% of m.p. 54–57°; recrystallization from ethanol gave a product of m.p. 60–61° (80%) (E., 61°). It could also be crystallized from ligroin.

Preparation of 3-chloro-4-methylacetophenone. The 4-methyl-3-nitroacetophenone prepared as above was reduced to the amino compound (which was not isolated) and was converted through the diazonium salt to the chloro compound, applying the "Organic Syntheses" (31) directions for making 3-chlorobenzaldehyde, and using 118 g. (0.66 mole) of 4-methyl-3-nitroacetophenone. Just prior to the diazotization, 300 ml. of acetic acid was added to serve as a solvent (this was done because in a trial run in which acetic acid was not used, considerable nitrous acid was lost, apparently because most of the compound being diazotized was present as a precipitate and was slow to dissolve). An excess of sodium nitrite [66 g. (0.96 mole) in 200 ml. of water] was added over six hours and the excess nitrite was destroyed by adding 13 g. (0.22 mole) of urea in 25 ml. of water. Upon standing overnight the product crystallized, it was filtered and recrystallized, twice from ethanol and once from ligroin; yield 60 g. (53%); m.p. 44–45° [W. and L. (55), 45–46°].

α-Bromo-3-chloro-4-methylacetophenone (not isolated). Ninety grams (0.56 mole) of bromine was added during a period of ninety minutes under stirring to 90 g. (0.53 mole) of the ketone in 500 ml. of petroleum ether (b.p. 35–60°); the mixture was then refluxed (water-bath at 50°) for four hours, when the evolution of hydrogen bromide had practically ceased; the remaining mixture was concentrated to 133 g. under reduced pressure. Since cooling in ice failed to yield a crystalline product, the residual dark liquor was dissolved in 300 ml. of acetone, treated with Darco, dried over sodium sulfate, filtered, and made up to a volume of 500 ml. with additional acetone. This solution was assumed to contain 0.44 mole of the bromomethyl ketone, and aliquots were reacted directly under nitrogen with two equivalents of the appropriate amine.

α-(3-Chloro-4-methylphenyl)-β-benzylmethylaminoethanol hydrochloride (*XVIIAc*) was made by Procedures 3L and 6Q; white needles. The intermediate amino ketone was isolated as the hydrochloride (see Table I), and a mixture melting point with XVIIAc resulted in a 15° depression.

XVIII. THE α-(2-CHLORO-4-METHYLPHENYL)-β-DIALKYLAMINOETHANOLS

2-Chloro-4-methylacetophenone, as starting material for the preparation of compounds in this series, was originally prepared in yields of approximately 50%, using the Friedel and Crafts reaction between acetyl chloride and 3-chlorotoluene

(57, 58; *cf.* also 59). In the present investigation acetic anhydride was used instead of acetyl chloride (54). Permanganate oxidation of the acetylation product to chloroterephthalic acid indicated that the reaction had given chiefly the desired compound. However, it must be assumed that the product obtained here was not entirely free from the structural isomer. Work was started toward the synthesis of a pure sample from 2-chloro-4-methylaniline through the nitrile but was postponed because the sample of the diamylamino alcohol already submitted for avian malaria screening tests, although active, was only one-third as active as quinine.

EXPERIMENTAL[6]

Preparation of 2-chloro-4-methylacetophenone. The method of Noller and Adams (54) was adapted to the preparation of this starting material. A 54% yield of the colorless liquid was obtained; b.p. 97–99° (4 mm.) or 239–241° (740 mm).

Permanganate oxidation of 5 g. of this ketone according to the method of Ganguly and Le Fèvre (58) yielded 4 g. of chloroterephthalic acid; m.p. 315°. One recrystallization from water gave the colorless acid of m.p. 316–317° (G. and Le F., 320°).

α-(2-Chloro-4-methylphenyl)-β-di-n-amylaminoethanol (XVIIIa). A mixture of an aliquot portion (0.1 mole) of the α-bromomethyl ketone solution and 32 g. (0.203 mole) of diamylamine was treated according to Procedures 3K and 5R (two vacuum fractionations). Evidence for the loss by displacement of some of the ortho halogen was obtained during the fractionations (*cf.* Section III); a significant quantity of diamylamine hydrochloride was isolated.

α-(2-Chloro-4-methylphenyl)-β-benzylmethylaminoethanol (XVIIIb). To an aliquot portion (0.2 mole) of the α-bromomethyl ketone solution was added 48.4 g. (0.4 mole) of benzylmethylamine; the reaction mixture was worked up according to Procedure 3L.

Reduction of 16 g. of the amino ketone hydrochloride by 200 ml. of 1.5 *N* aluminum isopropoxide was carried out according to Procedure 6R. The vacuum fractionation was carried out under an atmosphere of nitrogen, using a heated fractionating column.

XIX. THE α-(2-CHLORO-5-METHYLPHENYL)-β-DIALKYLAMINOETHANOLS

In the synthesis of this series of compounds an interesting observation was made. Reduction of the crude dioctylaminomethyl ketone in the form of the free base (not isolated) failed to yield a pure sample of the amino alcohol; however, when anhydrous aluminum chloride was added to the reduction mixture to furnish chloride ion, a satisfactory product was obtained. This result is to be compared with the observation (12) that the aluminumi sopropoxide reductions of the 4-bromo-α-dialkylaminoacetophenone hydrochlorides proceed in much better yields than the reduction of the free bases.

EXPERIMENTAL

2-Chloro-5-methylacetophenone was prepared according to Allen and Bridges (60) through the Friedel-Crafts reaction between acetic anhydride and 4-chlorotoluene.

α-Bromo-2-chloro-5-methylacetophenone was prepared according to Procedure 2 and was used without isolation.

α-(2-Chloro-5-methylphenyl)-β-di-n-octylaminoethanol (XIXa). An aliquot portion (0.6 mole) of the α-bromomethyl ketone and 289.5 g. (1.2 moles) of dioctylamine was treated according to Procedure 3K. The crude amino ketone (free base) (an oil) was dissolved in the reduction mixture and 40 g. (0.3 mole) of anhydrous aluminum chloride was added. The reaction was completed according to Procedure 9SR.

α-(2-Chloro-5-methylphenyl)-β-benzylmethylaminoethanol hydrochloride (*XIXb*). A mixture of an aliquot portion (0.2 mole) of the α-bromomethyl ketone solution and 48.4 g. (0.4 mole) of benzylmethylamine was worked up according to Procedure 3L. Thirty grams of the amino ketone hydrochloride (obtained after crystallization from absolute ethanol-ether) was treated with 300 ml. of 1 *N* aluminum isopropoxide and the experiment was completed according to Procedure 6Q. The amino alcohol hydrochloride was precipitated from dry ether by ethereal hydrogen chloride; colorless rectangular rods.

XX. THE α-(3-CHLORO-4-ETHOXYPHENYL)-β-DIALKYLAMINOETHANOLS

These compounds were prepared from *o*-chlorophenetole through the Friedel and Crafts reaction with chloroacetyl chloride followed by condensation of the product with secondary amines. In order to make certain that the side chain had entered the 4-position as expected, the product was degraded by oxidation and reduction to 4-ethoxybenzoic acid.

EXPERIMENTAL[6]

α,3-Dichloro-4-ethoxyacetophenone. The procedure followed here approximates standard practice [see Jörlander (61)]. Fifty grams (0.38 mole) of finely powdered aluminum chloride was added during thirty minutes to a rapidly-stirred mixture of 38 g. (0.33 mole) of chloroacetyl chloride and 52 g. (0.33 mole) of *o*-chlorophenetole dissolved in 100 ml. of carbon disulfide. After standing for another hour, the resulting thin syrup was poured with stirring into 500 ml. of ice-water containing 20 ml. of concentrated hydrochloric acid. The product was isolated by concentrating the carbon disulfide layer under reduced pressure; colorless needles, m.p. 58–60°, yield 30 g. (56% of the theoretical, allowing for 17 g. of *o*-chlorophenetole that was recovered by fractional distillation of the filtrate). Carrying out this reaction at an elevated temperature, or using more aluminum chloride, resulted in a lower yield of the desired product and the formation of much tar.

A pure sample of the compound was obtained by recrystallizations from petroleum ether; m.p. 78°.

Anal. Calc'd for $C_{10}H_{10}Cl_2O_2$: C, 51.52; H, 4.32.
Found: C, 51.28; H, 4.14.

3-Chloro-4-ethoxybenzoic acid. A small sample of the α,3-dichloro-4-ethoxyacetophenone was oxidized in an excess of sodium hypochlorite solution at room temperature and was recrystallized from 50% ethanol; colorless prisms, m.p. 210°.

Anal. Calc'd for $C_9H_9ClO_3$: C, 53.88; H, 4.52.
Found: C, 53.53; H, 4.54.

Reduction in alkaline solution with nickel-aluminum alloy (Raney catalyst powder) gave *4-ethoxybenzoic acid*; m.p. 194–195° [L. and B. (62), 195°].

α-(3-Chloro-4-ethoxyphenyl)-β-diethylaminoethanol hydrochloride (*XXAa*) was prepared according to Procedures 3HK and 5Q, using four equivalents of diethylamine, with petroleum ether (b.p. 30–65°) as the solvent; the mixture was allowed to stand overnight and was then refluxed for six hours to hasten the condensation.

α-(3-Chloro-4-ethoxyphenyl)-β-benzylmethylaminoethanol hydrochloride (*XXAc*) was prepared according to Procedures 3L and 6Q as colorless tablets. A mixture melting point of this and the hydrochloride of the amino ketone from which it was prepared resulted in a 15° depression.

XXI. α-(5-CHLORO-2-METHOXYPHENYL)-β-DIAMYLAMINOETHANOL

The first approach to this series, the acylation of 4-chloroanisole by the Friedel and Crafts reaction, following essentially the procedure of Wittig (63), and then brominating the product according to Procedure 2, was unsuccessful. The

second and successful approach consisted of condensing 4-chloroanisole with chloroacetyl chloride by the Friedel and Crafts reaction, under conditions which were essentially those employed by Jörlander (61); the condensation with diamylamine proceeded without difficulty and the resulting amino ketone was reduced to the amino alcohol in good yield.

EXPERIMENTAL

α-(5-Chloro-2-methoxyphenyl)-β-di-n-amylaminoethanol hydrochloride (*XXI*) was prepared according to Procedures 3JK and 5RQ, using 0.1 mole of α,5-dichloro-2-methoxyacetophenone [see Jörlander (61)] in 100 ml. of acetone. After adding the amine, it was found advantageous to replace the air in the flask with nitrogen. Acetone, rather than ether, was used in this step because the by-product diamylamine hydrochloride precipitated from this solvent as larger and more easily filterable crystals.

After purifying, the amino alcohol (pale yellow oil) was converted into the hydrochloride (white needles) by dissolving it in ether and adding ethereal hydrogen chloride.

XXII. THE α-(4-BROMO-3-METHYLPHENYL)-β-DIALKYLAMINOETHANOLS

The starting material, 4-bromo-3-methylacetophenone, was prepared from 2-bromotoluene and acetic anhydride exactly according to the directions of Noller and Adams (54) for the Friedel-Crafts reaction on 2-chlorotoluene, and it was identified by conversion into the oxime, which showed the same melting point as that reported by Borsche and Herbert (64, *cf.* also 59).

EXPERIMENTAL[6]

Preparation of 4-bromo-3-methylacetophenone. Careful fractionation gave a 45% yield of colorless oil; b.p. 119–125° (4–5 mm.); n_D^{20} 1.5738 ±5. Forty-six per cent of the starting material was recovered.

The *oxime* (64), colorless needles, precipitated slowly from ethanol; yield 60%; m.p. 108–109° (B. and H., 108°).

α,4-Dibromo-3-methylacetophenone was prepared according to Procedure 1D; colorless oil; yield 38%; b.p. 156–164° (1–2 mm.); n_D^{20} 1.6130 (not analyzed).

XXIII. α-(4-BROMO-2-METHYLPHENYL)-β-DI-*n*-AMYLAMINOETHANOL

The preparation of this compound was based on the Friedel-Crafts synthesis of the 4-bromo-2-methylacetophenone from 3-bromotoluene and acetic anhydride, following exactly the procedure of Noller and Adams (54) for making 4-chloro-3-methylacetophenone from 2-chlorotoluene. The identity and homogeneity of the sample of the acetylation product made in this investigation was not established; it is assumed that the orientation in the Friedel-Crafts reaction was in the main the same as in the original preparation by Claus (59, *cf.* also 64) using acetyl chloride.

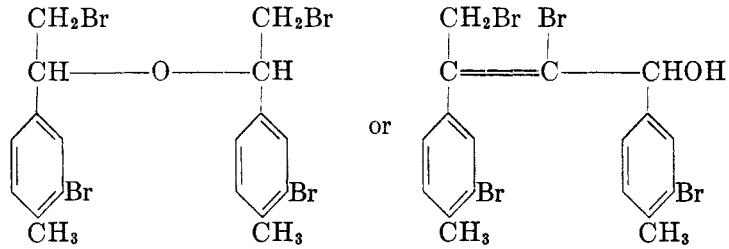
EXPERIMENTAL

α-(4-Bromo-2-methylphenyl)-β-di-n-amylaminoethanol (*XXIII*) was evaporated under reduced pressure onto a cold-finger condenser and then fractionally distilled under reduced pressure and an atmosphere of nitrogen, using a heated column. The product was a pale yellow oil.

XXIV. THE α-(3-BROMO-4-METHYLPHENYL)-β-DIALKYLAMINOETHANOLS

This synthesis utilized 3-amino-4-methylacetophenone (65), which was obtained from the nitro compound by reduction with stannous chloride. The Sandmeyer reaction gave the desired 3-bromo-4-methylacetophenone, which was readily brominated, and converted by aluminum isopropoxide reduction into the bromohydrin.

In the latter reaction a by-product was obtained, which from the analysis may be either of the following, the bromohydrin ether, or the product of an aldol condensation between two bromo ketone molecules and reduction of the remaining carbonyl (*cf.* Ref. 8).



There is analogy in the literature for both of these type reactions under the influence of aluminum isopropoxide (*cf.* Ref. 8). However, in the case of aldol condensation, steric hindrance would be expected to be insurmountable, and leads us to favor the former structure.

EXPERIMENTAL[6]

3-Amino-4-methylacetophenone. Reduction (*cf.* Ref. 31) of 66 g. of the 3-nitro compound (made as in Section XVII) by 1.2 moles of diaquo stannous chloride in 400 ml. of 1.2 *N* hydrochloric acid (slow heating) produced a sudden temperature rise from 43° to 70°, and a cooling bath was applied to check the reaction and to hold it at 70°.Heat was then applied to maintain the temperature at 65–70° for half an hour. Treatment with alkali gave 50 g. (92%); m.p. 77–79° (B. and D., 80°).

3-Bromo-4-methylacetophenone was obtained in 62% yield, following a procedure similar to that in "Organic Syntheses" (66a). Small-scale runs gave the better results. The product from steam distillation solidified (m.p. 41–43°) and after two crystallizations from 70% ethanol melted at 43°; rhombic plates.

Anal. Calc'd for C_9H_9BrO: C, 50.73; H, 4.26.
Found: C, 50.39; H, 4.56.

α,3-Dibromo-4-methylacetophenone was made in nearly quantitative yield by Procedure 1. After several crystallizations from ethanol it melted at 67–68°.

Anal. Calc'd for $C_9H_8Br_2O$: C, 37.02; H, 2.76.
Found: C, 36.85; H, 2.92.

α-Bromomethyl-3-bromo-4-methylbenzyl alcohol. (*cf.* Procedure 10). The reduction time was 10 minutes. The product distilled at 162–171° (3 mm.) and solidified; m.p. 47–49° (87%). Two crystallizations from ethanol and one from ligroin raised the melting point to 50°.

Anal. Calc'd for $C_9H_{10}Br_2O$: C, 36.76; H, 3.43.
Found: C, 36.79; H, 3.41.

A second reduction (one hour instead of 10 minutes) gave a 70% yield of the bromohy-

drin and a higher-boiling compound which was crystallized repeatedly from ethanol; m.p. 136–137°.

Anal. Calc'd for $C_{18}H_{18}Br_4O$: C, 38.06; H, 2.87.
$C_{18}H_{16}Br_4O$: C, 37.93; H, 3.18.
Found: C, 38.14; 38.04; H, 3.29; 3.59.

The di-n-butylamino alcohol (*XXIVa*) (Procedure 11RQ; condensation at 94° for 10 hours) distilled at 185–198° (2 mm.), and was converted into the hydrochloride from ether and recrystallized from a petroleum ether-acetone mixture by addition of ether. The *di-n-octylamino compound* (XXIVb) (Procedure 11R; condensation at 94° for 9 hours) was fractionally distilled (b.p. 262–272° at 2 mm.) and molecularly distilled twice at 135–140° under 10^{-2} mm. The hydrochloride (from ether) was extremely hygroscopic; it was recrystallized from ether (heating under pressure to dissolve).

XXV. THE α-3,4-DICHLOROPHENYL-β-DIALKYLAMINOETHANOLS

The amino alcohols, except the dicyclohexylamino compound, were prepared without difficulty by aluminum isopropoxide reduction of the amino ketones. When an attempt was made to prepare the dicyclohexylamino alcohol by the condensation with dicyclohexylamine, a reaction occurred with the formation of 70% of the theoretical amount of dicyclohexylamine hydrobromide; however, aluminum isopropoxide reduction of the resulting crude mixture gave none of the desired amino alcohol, and only dicyclohexylamine was isolated. The condensation with dicylohexylamine was effected, finally, through the bromohydrin, and this produced the desired amino alcohol directly, although in only 19% yield. The very low yield by this usually excellent method, and the absence of significant amounts of resinous by-products, is accounted for by assuming that the reaction proceeded first to the oxide, and that this conversion was complete and rapid, whereas the subsequent condensation of the secondary amine with the oxide to the amino alcohol was slow and incomplete in the time involved; the unreacted oxide, unexpected when this experiment was carried out, was undoubtedly lost in the vacuum distillation of the final product. The results of the reaction between dicyclohexylamine and α-bromomethyl-6,8-dichloro-2-phenyl-4-quinoline-methanol, where the oxide was formed and isolated under similar conditions (10), supports this conclusion.

EXPERIMENTAL[6]

α-Bromomethyl-3,4-dichlorobenzyl alcohol was prepared according to Procedure 10Z; it was crystallized from ligroin; 87% yield; m.p. 59–60°.

Anal. Calc'd for $C_8H_7BrCl_2O$: C, 35.59; H, 2.61.
Found: C, 36.06; H, 2.54.

α-3,4-Dichlorophenyl-β-n-octylaminoethanol hydrochloride (*XXVAh*) was prepared according to the Procedure 11T by heating a solution of 57.3 g. (0.44 mole) of monooctylamine and 30 g. (0.11 mole) of the bromohydrin in 175 ml. of dry toluene at 70–90° for nine hours. The mixture was then refluxed for seven hours. The toluene was removed by distillation under reduced pressure, and 300 ml. of absolute ether was added to the residue. The *n*-octylamine hydrobromide which separated was filtered; 23.3 g. (100%). The ether filtrate was extracted with four 250-ml. portions of 1 *N* hydrochloric acid and then with 200 ml. of water. The ether layer containing the hydrochloride was separated and cooled to 0°, and the white salt which then precipitated was filtered and dried. Two crystallizations from acetone gave 22 g. (56%); m.p. 227–229° dec.

α-3,4-Dichlorophenyl-β-dicyclohexylaminoethanol hydrochloride (*XXVAi*). Procedure 11Q was used. The light yellow oil which remained after evaporation of the ether was transferred to a small Claisen flask, and all of the material which was volatile below 100° at a pressure of 1 mm. (doubtless including 3,4-dichlorophenyl ethylene oxide) was distilled. In order effectively to remove all traces of dicyclohexylamine, 15 ml. of diphenyl ether was added to the residual oil, and the distillation was repeated. The crude hydrochloride which precipitated from ether was crystallized from ethyl acetate and then from 30:70 acetone-ligroin.

XXVI. THE α-2,4-DICHLOROPHENYL-β-DIALKYLAMINOETHANOLS

Several paths to the starting material, 2,4-dichloroacetophenone, were investigated. The Friedel-Crafts reaction on *m*-dichlorobenzene appeared to be impractical (67a). The action of methylmagnesium iodide on the 2,4-dichlorobenzoyl chloride, in spite of steric hindrance, which was expected to slow down somewhat the secondary reaction, gave a mixture of products, as also did dimethylcadmium. The synthesis was best accomplished through the nitrile by the addition of methylmagnesium iodide, and the yields in all of the steps starting from the acid chloride and going through the amide to the nitrile, were good except for the last step involving the addition of the Grignard reagent, where only a 25% yield was realized. The conversion from this point to the amino alcohols was accomplished through the bromo ketone and bromohydrin, which were obtained in good yields.

EXPERIMENTAL[6]

2,4-Dichlorobenzamide was obtained in 96% yield by the action of ice-cold aqueous ammonium hydroxide on the acid chloride; recrystallized from ethanol; m.p. 193–194°.

Anal. Calc'd for $C_7H_5Cl_2NO$: C, 44.24; H, 2.65.
Found: C, 44.20; H, 2.65.

2,4-Dichlorobenzonitrile, made originally from 2,4-dichloroaniline by the Sandmeyer reaction (68), was made here in 96% yield by the action of an excess of thionyl chloride on the amide (refluxing for eight hours); recrystallized from petroleum ether; m.p. 61–62° (G. and C., 61°).

A new preparation of 2,4-dichloroacetophenone. An ether solution (1.5 l.) of 188 g. (1.1 moles) of the above nitrile was added over five hours to 1.5 l. of ethereal 2.25 *N* methylmagnesium iodide (3.4 moles) under reflux, refluxing was continued for twelve hours, and the ether distilled. The reaction mixture was hydrolyzed by addition of 70 ml. of water and then 1270 g. of 77% sulfuric acid, breaking up the solid mass, refluxing for a short time, standing for twelve hours, again refluxing for a short time, and allowing to stand for an additional thirty-six hours; this was followed by addition of water and extraction of the product with ether. Fractional distillation under 22 mm. pressure gave 49 g. (25%) boiling at 132–135°; m.p. 30° [R. and T. (67), 33–34°]. The over-all yield from the acid was 16%.

α-Bromomethyl-2,4-dichlorobenzyl alcohol. A solution of 65.1 g. of the ketone in 250 ml. of absolute ether was brominated by adding 55 g. of bromine and moderating the temperature by a cooling bath as the reaction proceeded (over a half hour). After washing the solution with water and sodium bicarbonate, drying over sodium sulfate and distilling off the ether, the residue of crude bromo ketone (88 g.) was reduced with 310 ml. of 3 *N* aluminum isopropoxide (Procedure 10Y) (refluxing for twenty-two hours). The product

obtained from hydrolysis with 6 *N* sulfuric acid (87 g. of m.p. 53–56°) was recrystallized repeatedly from 80% ethanol (with Darco treatments); m.p. 72°.

Anal. Calc'd for $C_8H_7BrCl_2O$: C, 35.59; H, 2.61.

Found: C, 35.38; H, 2.48.

α-2,4-Dichlorophenyl-β-di-n-octylaminoethanol hydrochloride (*XXVIb*), was obtained by Procedure 11, with heating at 100° for twenty minutes and 140° for three hours. The excess dioctylamine was eliminated from an ether solution by fractional precipitation with standard ethereal hydrogen chloride; upon acidification by an excess of ethereal hydrogen chloride, the product crystallized very slowly on standing in the ice-box.

XXVII. THE α-2,5-DICHLOROPHENYL-β-DIALKYLAMINOETHANOLS

Lack of success in repeating the preparation of the starting material, 2,5-dichloroacetophenone, by the Friedel-Crafts reaction on *p*-dichlorobenzene (69), led to the development of an alternative method starting from 2,5-dichloroaniline through the Sandmeyer reaction to 2,5-dichlorobenzonitrile, essentially according to the method of Noelting and Kopp (70), and treatment of the nitrile with methylmagnesium iodide. We verified Noelting and Kopp's observation that successful diazotization depends upon strongly acid conditions and that the diazoamine is formed when dilute or weak acids are used as the solvent. In spite of complete diazotization, however, poor yields of the nitrile were obtained. An insoluble complex containing copper separates upon the addition of the diazonium salt solution to the cuprous cyanide; it is unusually stable to acids and boiling water, a fact which may account for the poor yields of nitrile.

The reaction between the nitrile and methylmagnesium iodide presented certain difficulties. Under a short reaction time and with concentrated reagents a white crystalline solid of m.p. 185–186° was obtained as the chief product; it was unaffected by boiling hydrochloric acid, contained 7.51% nitrogen, and therefore is not analogous to the triphenylpyridine of the type obtained by Ectors (71) in the reaction between benzonitrile and methylmagnesium iodide, a reaction which is favored by high concentration of the reactants. However, when the reagents were diluted and the reaction time lengthened, excellent yields of the methyl ketone were obtained.

It was characterized as the oxime, m.p. 130° [De C. (69), 130°], and as the new 2,4-dinitrophenylhydrazone.

No difficulty was experienced in bromination or in reduction of the bromomethyl ketone. The resulting bromohydrin reacted readily with secondary amines to form the amino alcohols.

EXPERIMENTAL[6]

2,5-Dichlorobenzonitrile (*cf.* 70). A solution of 160 g. (1 mole) of powdered 2,5-dichloroaniline in 40 ml. of 28% hydrochloric acid was rapidly chilled to 0° to precipitate the hydrochloride in finely divided form. A solution of 70 g. (1.02 moles) of sodium nitrite in 200 ml. of water was added over a period of one hour (0–5°) and the temperature was then allowed to rise to 15° where it was held for a half hour. The resulting clear dark brown solution was poured with rapid stirring into a solution of cuprous cyanide covered with two liters of benzene. After stirring the suspension for two hours, the benzene layer was

siphoned off, washed with water, dried, and treated with Norit. Evaporation of the benzene under reduced pressure gave 44 g. (25%) (m.p. 129–130°) which was sufficiently pure to use in the next step. It was crystallized from dilute ethanol.

A new preparation of 2,5-dichloroacetophenone. A solution of 13.5 g. (0.074 mole) of 2,5-dichlorobenzonitrile in 500 ml. of absolute ether was added dropwise over 2.5 hours to a refluxing solution of methylmagnesium iodide (prepared from 7.3 g. of magnesium and 70 g. of methyl iodide in 300 ml. of absolute ether). After refluxing for twenty-four hours, the mixture was hydrolyzed with ice and 300 ml. of concentrated hydrochloric acid. The ether extract was separated, washed with water, dried, and evaporated. The residual red oil was vacuum distilled at 3 mm.; b.p. 102–104°; yield 11.7 g. (83.5%).

The *2,4-dinitrophenylhydrazone* (new); m.p. 196–198° after repeated crystallizations from ethyl acetate.

Anal. Calc'd for $C_{14}H_{10}Cl_2N_4O_4$: N, 15.18. Found: N, 14.76.

α-Bromomethyl-2,5-dichlorobenzyl alcohol. The crude oily bromomethyl ketone, prepared according to Procedure 1B, was reduced to the bromohydrin according to Procedure 10. Treatment of the residue with dilute sulfuric acid left an oil which solidified on standing. The yield of light tan solid was 80% (calculated from the methyl ketone); m.p. 92–94°. After three crystallizations from ligroin it melted at 95–96°.

Anal. Calc'd for $C_8H_7BrCl_2O$: C, 35.59; H, 2.61.
Found: C, 36.02; H, 2.75.

XXVIII. THE α-3,5-DICHLOROPHENYL-β-DIALKYLAMINOETHANOLS

The preparation of 3,5-dichloroacetophenone by the addition of methylmagnesium iodide to 3,5-dichlorobenzaldehyde and oxidation of the resulting carbinol (72), was not feasible because of the unavailability of the starting material. The synthesis of this intermediate was therefore undertaken starting from *p*-aminoacetophenone.

Direct chlorination of *p*-aminoacetophenone was studied extensively in aqueous solution, in benzene, and in carbon tetrachloride. A great deal of resinification occurred and the only identifiable product isolated was *sym.*-trichloroaniline. Finally it was found that by absorbing a calculated weight of chlorine in cold acetic acid, and by adding this solution rapidly to a cold solution of *p*-aminoacetophenone in acetic acid, a 45% yield of 3,5-dichloro-4-aminoacetophenone could be obtained easily and consistently. Coloration was largely avoided by adding an excess of chipped ice to the reaction mixture immediately following the addition of the chlorine solution. The *sym.*-trichloroaniline which was formed as a by-product (29%) was separated by fractional crystallization from ethanol.

Bruining's deamination method (74) involving the refluxing of a mixture of the amine, sulfuric acid, ethanol, and sodium nitrite, gave yields of only 33% when applied to 3,5-dichloro-4-aminoacetophenone, probably because of extreme resistance to diazotization. It was necessary to resort to the diazotization method of Krishna and Bhatia (73), which involves the dropwise addition of a quinoline or pyridine solution of the amine to a solution of sodium nitrite in concentrated hydrochloric acid. Hypophosphorous acid reduction of the diazonium salt solution by the method of Mai (75, 76) proceeded smoothly and gave a yield of 80% of the deamination product. The boiling-ethanol reduction method also gave good yields (70%) but was less convenient because of the large volumes involved.

4-Amino-3-bromo-5-chloroacetophenone was made by bromination of the 4-amino-3-chloroacetophenone for the purpose of preparing 3-bromo-5-chlorophenyl amino alcohols, but the program was abandoned because of the disappointingly low activities of the 3,5-dibromophenyl types.

EXPERIMENTAL[6]

4-Acetylaminoacetophenone (77) was made by the action of acetic anhydride on 4-aminoacetophenone in water suspension. Attempts to chlorinate with calcium hypochlorite (bleach grade "HTH") by adding a 180 ml. solution of 20 g. to a solution of 13.5 g. of acetylaminoacetophenone in a mixture of 25 ml. each of ethanol, water, and concentrated acetic acid, gave a heavy oil which was converted spontaneously in an exothermic reaction into the *4-acetylamino-3-chloroacetophenone*, which solidified and was recrystallized from ethanol; yield 10 g.; m.p. 164° [Chattaway (78), 163°]. The use of an excess of "HTH" gave similar results but only the monochloro compound could be obtained. Other and more drastic conditions for achieving dichlorination failed. Hydrolysis with boiling 4 *N* hydrochloric acid (15% ethanol) (four hours), neutralization of the reaction mixture, extraction with ether, and crystallization from ethanol gave *4-amino-3-chloroacetophenone* in 88% yield; m.p. 91° (C., 92°).

4-Amino-3,5-dichloroacetophenone. A solution of 40 g. of chlorine in 500 ml. of concentrated acetic acid was added rapidly to a solution of 40 g. of 4-aminoacetophenone in 500 ml. of concentrated acetic acid; the temperature throughout was kept at 5°. Immediately following the mixing, the mixture was diluted with 2 l. of ice-water, and the resulting white precipitate was crystallized from 400 ml. of ethanol; 26 g. (44%); m.p. 162–163.5°.

Anal. Calc'd for $C_8H_7Cl_2NO$: N, 6.86. Found: N, 7.02.

From the filtrate upon addition of water was recovered 20 g. (29%) of *sym.*-trichloroaniline.

4-Amino-3-bromo-5-chloroacetophenone was prepared in 82% yield by bromination of the monochloro aminoacetophenone in acetic acid in the presence of sodium acetate (*cf.* 79); recrystallized from 85% ethanol; m.p. 168–169.5°.

Anal. Calc'd for $C_8H_7BrClNO$: C, 38.66; H, 2.84.
Found: C, 38.93; H, 2.93.

3,5-Dichloroacetophenone. A solution of 25 g. of the amine in 180 ml. of pyridine was added slowly to an ice-cold mixture of 18 g. of sodium nitrite in 400 ml. of concentrated hydrochloric acid (below 10°). When the addition was complete, and dilution of a sample with water gave no precipitate, 66 ml. of 50% hypophosphorous acid was added slowly, and stirring was continued for two hours; the temperature throughout was held below 5°. After standing overnight in the ice-box, the mixture was extracted with ether and this extract was washed, dried over sodium sulfate and distilled; the yield of oil was 18.5 g. (80%) of boiling range 107–110° (1 mm.); m.p. 26° [L. and B. (72), 26°].

α-Bromo-3,5-dichloroacetophenone (see Procedure 1). Crude yield (b.p. 135–150°/1 mm.), 96%. B.p. 148°/1 mm. Crystallized from ethanol; short hexagonal prisms; m.p. 73°.

In an identical experiment carried out several years later, the crude oily product after evaporation of the ether and standing in a refrigerator, crystallized in a *lower-melting form* which after repeated crystallizations from petroleum ether melted at 31.5–32.5°. When seeded with the higher-melting form the melting point of the sample rose to 71–72.5°. Attempts to convert this back into the low-melting form were unsuccessful.

An alternative and probably superior preparative procedure utilized conc'd acetic acid as the reaction solvent and precipitation of the product by means of ice; one crystallization from 95% ethanol gave a 68% yield of nearly pure material melting at 70–71.5°.

Anal. Calc'd for $C_8H_5BrCl_2O$: C, 35.86; H, 1.88.
Found: C, 35.89; H, 1.98.

XXIX. α-2,6-DICHLOROPHENYL-β-DI-*n*-OCTYLAMINOETHANOL

2,6-Dichloroacetophenone, made according to Lock and Böck (72), was brominated, and without isolation of the bromomethyl ketone was reduced to the bromohydrin in an over-all yield of 18% from the methyl ketone. The low yield was not surprising in view of the steric effect of the two ortho chlorine atoms.

EXPERIMENTAL[6]

α-Bromomethyl-2,6-dichlorobenzyl alcohol. The crude bromomethyl ketone, prepared according to Procedure 1B, was reduced to the bromohydrin, using Procedure 10Z. The oil obtained after treatment of the residue with dilute sulfuric acid was fractionated at 2 mm. pressure, and the fraction boiling at 135–142° was refractionated twice at 1 mm. The fraction boiling at 136–137° represented a yield of 18% (calculated from the methyl ketone); n_D^{28} 1.5950.

Anal. Calc'd for $C_8H_7BrCl_2O$: C, 35.59; H, 2.61.
Found: C, 35.45; H, 2.59.

α-2,6-Dichlorophenyl-β-di-n-octylaminoethanol hydrochloride (XXIX). A solution of 20 g. (0.072 mole) of the bromohydrin and 42 g. (0.173 mole) of dioctylamine in 75 ml. of dry xylene was refluxed for six hours. The mixture was diluted with ether, cooled, and the dioctylamine hydrobromide was filtered; 22.5 g. (93%). The solvent and excess dioctylamine were removed by distillation under 1 mm. pressure. The residual oil was dissolved in dry ether and the hydrochloride was precipitated in four fractions with ethereal hydrogen chloride. The first two fractions melting between 96–100° were combined and crystallized from an ether-ethanol mixture; yield 7 g. (21%); m.p. 98–99.5°.

XXX. THE α-3,5-DIBROMOPHENYL-β-DIALKYLAMINOETHANOLS

A portion of the 3,5-dibromoacetophenone employed here as starting material was obtained by an improvement in the procedure for diazotization and reduction (74) of 4-amino-3,5-dibromoacetophenone (79). Our procedure, using pyridine as the reaction solvent, had one operational advantage in that steam distillation proved to be unnecessary, and the yield was brought to 72%.

The diamylamino ketone appeared to be very unstable, and satisfactory results could not be obtained on reduction; consequently the preparation of this amino alcohol was carried out through the bromohydrin obtained by aluminum isopropoxide reduction of the bromomethyl ketone.

EXPERIMENTAL[6]

Preparation of 3,5-dibromoacetophenone. The method of Krishna and Bhatia (73; *cf.* also 80) was adapted and modified slightly for the diazotization of 4-amino-3,5-dibromoacetophenone. To a well-stirred solution of 20 g. of sodium nitrite in 400 ml. of concentrated hydrochloric acid (cooled to 10°) was added dropwise a solution of 33 g. (0.11 mole) of 4-amino-3,5-dibromoacetophenone in 200 ml. of pyridine. During the addition (requiring about two hours), the reaction temperature was maintained under 10°. The diazonium salt was reduced by the method of Mai (75, 76). The orange colored product melted at 55–58°; 22 g. (72%). After vacuum distillation [b.p. 160–164° (1–2 mm.)] it melted at 60–61°; and after one recrystallization from ethanol, it melted at 64–65° [B. (74), 65°].

α-3,5-Tribromoacetophenone was prepared according to Procedure 1A, using artificial light or gaseous hydrogen bromide to start the reaction. Evaporation of the reaction sol-

vent gave a quantitative yield of almost colorless material; m.p. 78–80°. Recrystallization from ethanol gave colorless needles (67%) of m.p. 84–85°; two additional crystallizations brought the melting point to 85–86°.

Anal. Calc'd for $C_8H_5Br_3O$: C, 26.92; H, 1.41.
Found: C, 26.92; H, 1.52.

α-Bromomethyl-3,5-dibromobenzyl alcohol (the bromohydrin). Ninety grams (0.25 mole) of α-3,5-tribromoacetophenone in 300 ml. of dry isopropanol was reduced with 250 ml. of 3 *N* aluminum isopropoxide according to Procedure 10Y. The product solidified upon evaporating the ether solution, and was recrystallized from ethanol (with Darco treatment); 38 g. (53%); m.p. 77–80°. Several additional recrystallizations yielded colorless rods of m.p. 82–83°; a mixture m.p. with the α-bromomethyl ketone (m.p. 85–86°) was 60–68°.

Anal. (91) Calc'd for $C_8H_7Br_3O$: Br, 66.81. Found: Br, 67.23.

α-3,5-Dibromophenyl-β-diethylaminoethanol hydrochloride (XXXAa). Twenty-two grams (0.3 mole) of diethylamine was added to a solution of 53.5 g. (0.15 mole) of α-3,5-tribromoacetophenone in dry ether (see Procedure 3L). The amino ketone hydrochloride (hygroscopic) melted at 153–157°. The reduction according to Procedure 6Q gave colorless rods.

α-3,5-Dibromophenyl-β-di-n-amylaminoethanol hydrochloride (XXXAb). A mixture of 35.9 g. (0.1 mole) of the crude bromohydrin, 31 g. (0.2 mole) of diamylamine, and 125 ml. of dry xylene was heated under reflux for seven hours (see Procedure 11SQ). The red oil obtained upon concentration of the ether extract was evaporated under reduced pressure onto a cold-finger condenser. A few grams of crystalline material was collected in the first fraction; m.p. 60–65°. This material was not the bromohydrin, as shown by a mixture melting point depression, and it could not have been the ethylene oxide because under the high temperature it would not have escaped reaction. Doubtless it is the 3,5-dibromoacetophenone (m.p. 65°) resulting from hydramine fission, but a mixture melting point identification was not made. The other fractions (15 g. of yellowish oil) were dissolved in dry ether; addition of ethereal hydrogen chloride precipitated 15 g. of crystalline hydrochloride.

Pyrolysis (bath temperature 300–312°) of the hydrochloride produced the secondary amine hydrochloride in excellent yield. However, attempts to isolate the other fragment of hydramine fission, 3,5-dibromoacetophenone, failed.

α-3,5-Dibromophenyl-β-benzylmethylaminoethanol (XXXAc). Reduction of 36 g. (0.083 mole) of the amino ketone hydrochloride with 300 ml. of 1 *N* aluminum isopropoxide was performed according to Procedure 6SR. Attempts to form a crystalline hydrochloride failed. The product was first evaporated under reduced pressure onto a cold-finger condenser and then fractionated at a pressure of 2 mm. under a stream of nitrogen, using a heated 8-inch Vigreux column.

XXXI. α-2,4-DIISOPROPYLPHENYL-β-DIETHYLAMINOETHANOL

EXPERIMENTAL[6]

2,4-Diisopropylacetophenone. An equimolar mixture of acetyl chloride and 1,3-diisopropylbenzene was introduced dropwise into a cooled mixture of 1.4 moles of anhydrous aluminum chloride and carbon disulfide over a period of eight hours. After removing the solvent under reduced pressure, the residue was poured onto cracked ice and extracted with ether. The colorless product distilled at 93–96° (1–2 mm.); n_D^{24} 1.5108–1.5113. The yields in two runs were 81 and 87% respectively. The orientation in the Friedel-Crafts reaction here was assumed.

Anal. Calc'd for $C_{14}H_{20}O$: C, 82.30; H, 9.87.
Found: C, 83.01; H, 10.20.

XXXII. THE α-CARVACRYL-β-DIALKYLAMINOETHANOLS

All except one of the compounds in this series were prepared by the usual scheme starting from 2-acetyl-*p*-cymene. One tertiary alcohol, namely, α-carvacryl-α-*n*-propyl-β-diethylaminoethanol, was prepared from the diethylamino ketone by reaction with *n*-propylmagnesium bromide.

EXPERIMENTAL[6]

The *dibutylamino* compound (XXXIIAb) distilled at 171–175° under 4 mm. The hydrochloride was formed by dissolving the free base in acetone, acidifying with ethereal hydrogen chloride and diluting with ether.

β-Piperidyl- and β-morpholinyl-α-carvacrylethanol hydrochlorides (*XXXIIAc, d*). The amino ketones (free bases) were liberated from the hydrochlorides with sodium hydroxide, and the resulting oils (isolated from the ether extracts) were reduced according to Procedure 5Q. The products were precipitated from acetone by acidification with ethereal hydrogen chloride.

α-Carvacryl-α-n-propyl-β-diethylaminoethanol (*XXXIIAe*). A solution of α-diethylamino-5-isopropyl-2-methylacetophenone was prepared from 0.5 mole of the bromomethyl ketone by overnight treatment at room temperature with an excess of diethylamine in ether. The diethylamine hydrobromide was filtered, the filtrate was washed with saturated sodium chloride, and the ethereal solution was dried. This dried solution was added to 145 ml. of 2.5 *N* *n*-propylmagnesium bromide rapidly enough to maintain gentle refluxing. The mixture was stirred for two hours and then hydrolyzed with 130 ml. of 6 *N* hydrochloric acid and ice. The aqueous layer was made alkaline and repeatedly extracted with ether. The ether extract was dried over sodium sulfate and the ether was evaporated. The residue was fractionally distilled several times under a pressure of 5 mm.

XXXIII. THE α-(2,4-DICHLORO-3-METHYLPHENYL)-β-DIALKYLAMINOETHANOLS

In this series 2,6-dichlorotoluene was employed as starting material. A Friedel-Crafts reaction using acetyl chloride yielded 2,4-dichloro-3-methylacetophenone. The structure of this was proved by oxidation to a dichloroisophthalic acid (2, 4), which upon catalytic-reductive dehalogenation with palladium-black yielded isophthalic acid.

The 2,4-dichloro-3-methylacetophenone was brominated in ether, and aluminum isopropoxide reduction produced α-bromomethyl-2,4-dichloro-3-methylbenzyl alcohol, which in turn was condensed with secondary amines to give the desired amino alcohols.

EXPERIMENTAL[6]

2,4-Dichloro-3-methylacetophenone. A stirred mixture of 346 g. of 2,6-dichlorotoluene and 280 g. of powdered anhydrous aluminum chloride was heated on a boiling water-bath, and 162 g. of acetyl chloride was added slowly. Heating was continued for 2.5 hours, and the complex was then hydrolyzed by pouring over an ice-hydrochloric acid mixture. The resulting pasty solid was filtered, dried, and purified by distillation *in vacuo*; b.p. 147–148° (10 mm.); m.p. 38°; yield 195 g. (45%).

Anal. Calc'd for $C_9H_8Cl_2O$: C, 53.23; H, 3.97.
Found: C, 53.48; H, 3.87.

Proof of structure. A mixture of 5 g. of the above acetophenone derivative, 200 ml. of water, 20 g. of potassium permanganate, and 5 ml. of 50% sodium hydroxide was heated under reflux for three hours, after which time 25 ml. of water was distilled off in order to remove any remaining starting material. After the reaction mixture had cooled, the manganese dioxide was filtered off, and the filtrate was acidified with hydrochloric acid

and evaporated to dryness. The resulting crude dichloroisophthalic acid (2,4) was reductively dehalogenated by palladium-Darco hydrogenation in dilute acid solution; needles; m.p. 344°; a mixture melting point with isophthalic acid showed no depression.

2,4-Dichloro-3-methylphenacyl bromide. This compound was prepared according to Procedure IA. Forty-two grams of bromine was added slowly to a stirred solution of 53 g. of 2,4-dichloro-3-methylacetophenone in 150 ml. of dry ether. The ether was then distilled off and the remaining oil distilled under reduced pressure. The material exhibited a tendency to remain as a supercooled liquid after distillation; b.p. 167–169° (8 mm.); m.p. 61°; yield 60 g. (82%).

Anal. Calc'd for $C_9H_7BrCl_2O$: C, 38.33; H, 2.51.
Found: C, 38.08; H, 2.52.

α-Bromomethyl-2,4-dichloro-3-methylbenzyl alcohol. The preparation of this compound was essentially the same as given in Procedure 10, using 60 g. of 2,4-dichloro-3-methylphenacyl bromide and 400 ml. of 1.5 *N* aluminum isopropoxide. Reduction was complete in ten hours. After evaporation of the excess isopropanol under reduced pressure the reaction mixture was hydrolyzed with 6 *N* sulfuric acid. The resulting solid was filtered, washed with water, dried, and recrystallized from petroleum ether; m.p. 114°; yield 50 g. (83%).

Anal. Calc'd for $C_9H_9BrCl_2O$: C, 38.06; H, 3.19.
Found: C, 38.05; H, 3.22.

α-(2,4-Dichloro-3-methylphenyl)-β-di-n-butylaminoethanol (XXXIIIa). A solution of 50 g. of 2,4-dichloro-3-methylphenacyl bromide in 200 ml. of dry ether was added slowly to an ice-cold solution of 48 g. of dibutylamine in 200 ml. of dry ether (Procedure 3M). After the addition, the solution was stirred for four hours at room temperature, the dibutylamine hydrobromide was filtered off, and the ether evaporated *in vacuo* under nitrogen at room temperature. The oil was converted into a hydrochloride, which was then reduced without purification, according to Procedure 7R, using 450 ml. of 1.1 *N* aluminum isopropoxide. After reducing for five hours, the excess isopropanol was evaporated under reduced pressure, and the remaining oil hydrolyzed with 50% sodium hydroxide.

After extracting into ether and drying, the oil was distilled *in vacuo* under nitrogen.

α-(2,4-Dichloro-3-methylphenyl)-β-di-n-amylaminoethanol (XXXIIIb). (Procedure 11R). A mixture of 40 g. of α-bromomethyl-2,4-dichloro-3-methylbenzyl alcohol, 45 g. of dibutylamine, and 150 ml. of dry xylene was refluxed for twelve hours and cooled. Ether was added and the dibutylamine hydrobromide filtered. The filtrate was washed with 10% sodium hydroxide, then with water, and was dried over sodium sulfate. After evaporating the solvent an oil remained, which was fractionally distilled *in vacuo* under nitrogen.

α-(2,4-Dichloro-3-methylphenyl)-β-di-n-octylaminoethanol hydrochloride (XXXIIIc). Following Procedure 11RQ, 50 g. of α-bromomethyl-2,4-dichloro-3-methylbenzyl alcohol and 125 g. of dioctylamine were used with no added solvent. After heating at 130° for four hours, the mixture was cooled, diluted with ether, and the dioctylamine hydrobromide filtered. The filtrate was washed once with 30% sodium hydroxide and twice with water. After drying the solution over sodium sulfate, the ether was evaporated, and the remaining oil distilled *in vacuo* under nitrogen. The base was converted into the hydrochloride in a mixture of ether and petroleum ether, and this was recrystallized from ethyl acetate.

α-(2,4-Dichloro-3-methylphenyl)-β-benzylmethylaminoethanol hydrochloride (XXXIIId). Procedure 11RQ was followed using 50 g. of α-bromomethyl-2,4-dichloro-3-methylbenzyl alcohol, 43 g. of benzylmethylamine and 150 ml. of dry benzene. The reaction mixture was heated under reflux for eight hours, and the product was isolated according to the procedure given for XXXIIIc.

XXXIV. THE α-(4,5-DICHLORO-2-METHYLPHENYL)-β-DIALKYLAMINOETHANOLS

The starting material for this series was 3,4-dichlorotoluene. The Friedel-Crafts reaction with acetyl chloride gave 4,5-dichloro-2-methylacetophenone,

the structure of which was shown (a) by oxidation to the known 4,5-dichlorophthalic acid (81), and (as further confirmation) (b) by catalytic reduction of this to phthalic acid.

The 4,5-dichloro-2-methylacetophenone was converted by bromination in ether to the α-bromomethyl ketone, which was then reduced by aluminum isopropoxide to α-bromomethyl-4,5-dichloro-2-methylbenzyl alcohol. The desired amino alcohols were obtained by subsequent condensations with the appropriate secondary amines.

EXPERIMENTAL[6]

4,5-Dichloro-2-methylacetophenone. To a stirred solution of 320 g. of 3,4-dichlorotoluene and 260 g. of powdered anhydrous aluminum chloride (heated on a boiling water bath) was added slowly 150 g. of acetyl chloride. After heating for an additional three hours, the material was hydrolyzed by pouring into an ice-hydrochloric acid mixture. The resulting waxy solid was filtered, dried, and distilled under reduced pressure; b.p. 125–127° (2 mm.); m.p. 55° (after two recrystallizations from ethanol); yield 243 g. (60%).

Anal. Calc'd for $C_9H_8Cl_2O$: C, 53.23; H, 3.97.
Found: C, 53.10; H, 4.04.

The proof of structure was carried out as in the case of 2,4-dichloro-3-methylacetophenone (see Section XXXIII) by oxidation to the known 4,5-dichlorophthalic acid; m.p. 202° [V. (79), about 200° under rapid heating]. Catalytic reductive dehalogenation gave phthalic acid.

4,5-Dichloro-2-methylphenacyl bromide was made essentially by Procedure 1A, using 240 g. of 4,5-dichloro-2-methylacetophenone dissolved in 900 ml. of dry ether, with slow addition of 191 g. of dry bromine. The ether was distilled off, and the residual oil was distilled under reduced pressure; yield 284 g. (85%); b.p. 156° (2 mm.). Two recrystallizations from ethanol gave a sample melting at 73–74°.

Anal. Calc'd for $C_9H_7BrCl_2O$: C, 38.33; H, 2.51.
Found: C, 38.06; H, 2.39.

α-Bromomethyl-4,5-dichloro-2-methylbenzyl alcohol (the bromohydrin). Procedure 10Y was employed, using 76 g. of 4,5-dichloro-2-methylphenacyl bromide and 680 ml. of 1.24 *N* aluminum isopropoxide. Reduction was complete in seven hours, after which the excess isopropanol was evaporated under reduced pressure and the residual material hydrolyzed with 6 *N* sulfuric acid. The solid was filtered, washed with water, dried, and recrystallized from petroleum ether; yield 47.5 g. (62%). Three recrystallizations gave a sample melting at 103°.

Anal. Calc'd for $C_9H_9BrCl_2O$: C, 38.06; H, 3.19.
Found: C, 38.42; H, 3.14.

The *amino alcohols* were prepared according to the procedures indicated in Table I. The vacuum fractionations were carried out under an atmosphere of nitrogen. In the case of the *dioctylamino alcohol*, a crystalline hydrochloride could be obtained by neutralizing an ethyl acetate solution of the pure base with ethereal hydrogen chloride, heating to boiling, and allowing to cool slowly.

XXXV. THE α-4-CHLOROPHENYL-β-ALKYL-β-DIALKYLAMINOETHANOLS

In this series the amino alcohols were prepared with three different β-alkyl groups, methyl, ethyl, and *n*-butyl. 4-Chloropropiophenone (commercially available), 4-chlorobutyrophenone, and 4-chlorocaprophenone, respectively, were chosen as starting materials.

The α-bromo ketones were made and used directly, without isolation, in ether solution. A small sample of α-bromo-4-chloropropiophenone (one of the

strongest lachrymators encountered in this work) was isolated, and shown to be identical in its properties with the compound obtained by Collet (17) in the Friedel-Crafts reaction between chlorobenzene and α-bromopropionyl chloride.

Evidence for the displacement of nuclear halogen was obtained during the distillation of two amino alcohols (XXXVAa and b); in this operation there were produced and isolated significant quantities of the secondary amine hydrochlorides (*cf.* Section III).

EXPERIMENTAL[6]

4-Chlorobutyrophenone was prepared according to Morgan and Hickinbottom (82) in 78% yield.

4-Chlorocaprophenone. A well-stirred mixture of 225 g. (2 moles) of chlorobenzene, 600 g. of carbon disulfide, and 250 g. (1.87 moles) of anhydrous aluminum chloride, was heated on a steam-bath until refluxing started, and 300 g. (2.2 moles) of caproyl chloride was added slowly over a period of one hour. Refluxing was continued for an additional hour. The solvent was distilled off, and the cooled residue was hydrolyzed in ice and hydrochloric acid. The resulting solid was recrystallized from ethanol; 270 g. (65%); m.p. 61.5–62.5°. The orientation here was assumed.

Anal. Calc'd for $C_{12}H_{15}ClNO$: C, 68.40; H, 7.18.
Found: C, 68.14; H, 7.14.

Preparation of α-bromo-4-chloropropiophenone. 4-Chloropropiophenone was brominated according to Procedure 2. The solvent was evaporated from a small portion, and recrystallization of the crude material from ethanol (with Darco treatment) gave colorless cubes of m.p. 78–79° [C. (17), 77.5°].

XXXVI. THE α-4-BROMOPHENYL-β-METHYL-β-DI-*n*-ALKYLAMINOETHANOLS

EXPERIMENTAL[6]

Preparation of 4-bromopropiophenone was carried out according to the procedure given for the preparation of 4-chlorocaprophenone (see Section XXXV) (*cf.* 83, 84). A 38% yield was obtained; m.p. 45–46° [E. and L. (84), 47°].

α-4-Dibromopropiophenone was prepared according to Procedure 1A; yield 65%; m.p. 84–84.5° (not analyzed).

XXXVII. α-(4-BROMO-3-METHYLPHENYL)-β-METHYL-β-BENZYLMETHYLAMINOETHANOL

4-Bromo-3-methylpropiophenone employed as the starting material, was obtained by the Friedel-Crafts reaction between propionyl chloride and 2-bromotoluene. The orientation is assumed here and is based on analogy to the acetylation of 2-bromotoluene (see Section XXII). It is doubtful however, that the products obtained here are entirely free from the structural isomer.

EXPERIMENTAL[6]

4-Bromo-3-methylpropiophenone. Two moles of propionyl chloride was added slowly under mechanical stirring and gentle refluxing, to a mixture of two moles of 2-bromotoluene, 2 moles of anhydrous aluminum chloride, and 800 ml. of carbon disulfide. The product was worked up according to the usual procedure (54), and vacuum distillation gave 170 g. (38%); colorless oil; b.p. 109–110° (1–2 mm.); n_D^{20} 1.5611 (not analyzed).

An ethereal solution of *α-4-dibromo-3-methylpropiophenone* was prepared according to Procedure 2.

α-(4-Bromo-3-methylphenyl)-β-methyl-β-benzylmethylaminoethanol (*XXXVII*). To the aliquot portion (0.2 mole) of the α-bromomethyl ketone was added 84.4 g. (0.4 mole) of benzylmethylamine; the reaction mixture was worked up according to Procedure 3L. The resulting amino ketone hydrochloride (27 g. of m.p. 172–175°) was reduced according to Procedure 6U, and the amino alcohol crystallized from ethanol as colorless rectangular rods.

XXXVIII. SOME ARYL AMINO KETONES AND AMINO ALCOHOLS CARRYING THE CAPRYL CHAIN

A few representative amino alcohols and amino ketones were made from caprophenone and the para-ethyl, para-isopropyl and para-*tert.*-butyl homologs. The last three ketones were made by the Friedel-Crafts reaction between caproyl chloride and ethyl-, isopropyl- and *tert.*-butylbenzenes, respectively. The amino alcohols in these series may exist in stereoisomeric forms. The few compounds obtained as oils doubtless were mixtures. In the case of those obtained as crystalline hydrochlorides, the compounds prepared for test appeared to be homogeneous, but no attempt was made to obtain the pure stereoisomers.

EXPERIMENTAL[6]

β-(Di-n-butylamino)-α-phenylhexanol (*XXXVIIIAa*). The α-bromocaprophenone was prepared from caprophenone according to Procedure 2 and treated with dibutylamine in ether (thirty hours), the reaction proceeding very slowly (incomplete). The crude amino ketone was obtained as an oily residue and was reduced by Procedure 5; the product distilled under 4 mm. at 185–186°; redistillation gave cuts of n_D^{20} 1.4918–1.4920; 11 g. (16%).

α-(N-Piperidyl)caprophenone hydrochloride (*XXXVIIIBa*) was prepared like the α-morpholinylcaprophenone hydrochloride (below), and was recrystallized twice from acetone.

α-(N-Morpholinyl)caprophenone hydrochloride (*XXXVIIIBb*). Reaction between an aliquot portion of the ether solution of α-bromocaprophenone (Procedure 2) and an excess of morpholine (twenty-four hours at room temperature) gave an oil which was converted into a crystalline hydrochloride from acetone by the addition of ethereal hydrogen chloride (yield calculated from caprophenone was 84%); m.p. 188–190°. It was crystallized twice from acetone.

β-(N-Morpholinyl)-α-phenylhexanol hydrochloride (*XXXVIIIAc*) was prepared by reduction of the amino ketone (Procedure 5), and the oil obtained crystallized from acetone upon addition of ethereal hydrogen chloride. The product showed a marked mixture melting point depression with the amino ketone hydrochloride. The yield was 16 g.; m.p. 207–210°; it was recrystallized three times by solution in hot methanol, and addition of dry ether and cooling; m.p. 215–217°.

A second crop of crystals was obtained from the mother liquors of the first crystallization (35 g.; m.p. 140–142°); presumably this is either the stereoisomer or a mixture of stereoisomers; it was recrystallized once from methanol by addition of dry ether; m.p. 140°.

Anal. Calc'd for $C_{16}H_{25}NO_2 \cdot HCl$: C, 64.09; H, 8.74.
Found: C, 63.81; H, 9.00.

4-Ethylcaprophenone was prepared exactly according to the procedure described for the 4-*tert.*-butyl analog. The product distilling at 150–155° (8–10 mm.) was 222 g. (83%). Redistillation gave a cut of n_D^{24} 1.5103. The orientation was assumed.

Anal. Calc'd for $C_{14}H_{20}O$: C, 82.30; H, 9.87.
Found: C, 82.08; H, 10.04.

β-(Di-n-butylamino)-α-(4-ethylphenyl)hexanol (*XXXVIIIAd*) was prepared through

α-bromo-4-ethylcaprophenone (not isolated) and aluminum isopropoxide reduction of the crude amino ketone by a procedure identical with that described for the 4-*tert.*-butyl analog (Procedures 3K and 5TR). The product was fractionally distilled at 1–2 mm.; yield 12.7 g. (19%), from which cuts of b.p. 140–150° were taken for analysis and test; n_D^{25} 1.4830–1.4836. Doubtless this was a mixture of stereoisomers.

4-Isopropylcaprophenone was made in the same way as 4-*tert.*-butylcaprophenone (see below). However, here the reaction temperature was maintained at 10° during the addition, and then the reaction mixture was stirred at room temperature for four hours. The yield was 87%; b.p. 168–176° (12–13 mm.). The orientation was assumed (not analyzed).

The *oxime* crystallized from dilute ethanol as colorless needles of m.p. 54–55°.

Anal. Calc'd for $C_{15}H_{23}NO$: N, 6.01. Found: N, 6.11.

4-tert.-Butylcaprophenone was prepared by dropwise addition over eight hours of 105 g. (0.81 mole) of *tert.*-butylbenzene and 108 g. (0.81 mole) of caproyl chloride with stirring into a mixture of 106 g. (0.8 mole) of anhydrous aluminum chloride and 150 ml. of carbon disulfide maintained at 23°. The mixture was heated to reflux, allowed to stand for twelve hours, and hydrolyzed in ice and hydrochloric acid. Fractional distillation gave a nearly pure material; 134 g. (71%); redistillation gave a cut of b.p. 120–130°; n_D^{25} 1.5065.

Anal. Calc'd for $C_{16}H_{24}O$: C, 82.70; H, 10.41.
Found: C, 82.65; H, 10.67.

α-(4-tert.-Butylphenyl)-β-(diethylamino)hexanol hydrochloride (XXXVIIIAf). A solution of 47 g. (0.2 mole) of 4-*tert.*-butylcaprophenone in 300 ml. of ether was allowed to react with 32 g. (0.2 mole) of bromine, added slowly with preliminary heating to initiate reaction. The solution was washed, dried over sodium sulfate, and treated with 29.2 g. (0.4 mole) of diethylamine at room temperature (six days). The red solution was filtered from diethylamine hydrobromide (97% yield) and evaporated. The resulting red oil was reduced by aluminum isopropoxide according to Procedure 5R; three cuts were taken of n_D^{25} 1.4963, 1.4959, and 1.4960 (15.5 g.; 24%). It was converted into the hydrochloride from ether, and crystallized three times from ethyl acetate.

XXXIX. SOME AMINO KETONES AND ALCOHOLS MADE FROM LAUROPHENONE

It seemed of interest to prepare some representative compounds in this series where the low nuclear molecular weight (of the phenyl group) was partly compensated by a long carbon chain, carrying the amino alcohol group in the proper location next to the aryl group. These compounds were of interest also for comparison with the completely aliphatic amino alcohols made from lauric acid (85).

Laurophenone was brominated in carbon tetrachloride. The α-bromo ketone in ether reacted slowly with the secondary amines, diethylamine, piperidine, and morpholine, but only the amino ketones from the latter two amines were obtained as crystalline hydrochlorides.

Reduction of the amino ketones was found to be accomplished best by the aluminum isopropoxide method, but mixtures of stereoisomers invariably resulted. One stereoisomer was usually obtainable in a pure state by fractional recrystallizations, and the tests were carried out only on what appeared to be homogeneous samples. Because of the lack of time little effort was made to obtain the more difficultly isolable stereoisomers for comparison. It is noteworthy that in one case, namely α-piperidyllaurophenone, reduction by sodium and alcohol was successful and gave as the chief product the same compound as was obtained in the aluminum isopropoxide reduction.

Laurophenone was used in a typical Mannich reaction which proceeded satisfactorily but very slowly, and the β-dimethylamino ketone (XXXIXD) was obtained in 43% yield. Since the diethylamino analog was considered to be a better choice for screening tests, an attempt was made to make the corresponding amino ketone and to reduce this to the amino alcohol. However, the amino ketone was not easily obtained and it was not isolated in crystalline form; it was used in the crude condition, however, and was reduced with aluminum isopropoxide to the amino alcohol (XXXIXB), which was obtained in very small yield as a crystalline hydrochloride. Only the one form was isolated although a stereoisomer is of course possible.

EXPERIMENTAL[6]

α-Bromolaurophenone. Laurophenone (32 g.) in 150 ml. of carbon tetrachloride was treated dropwise with 21 g. of bromine in 50 ml. of the same solvent; evaporation gave an oil which crystallized; it was recrystallized from ethanol; 32 g. (78%); m.p. 29–30°.

Anal. Calc'd for $C_{18}H_{27}BrO$: C, 63.71; H, 8.02.
Found: C, 63.88; H, 8.30.

2-Diethylamino-1-phenyldodecanol-1 hydrochloride (XXXIXAa). Numerous variations in the condensation between diethylamine and α-bromolaurophenone failed to yield a crystalline hydrochloride of the amino ketone. The best results were obtained in the cold but the reaction was very slow and incomplete under the conditions finally chosen. A reaction mixture of 18 g. of α-bromolaurophenone and 50 ml. of diethylamine was allowed to stand in the refrigerator for one week and was filtered from diethylamine hydrobromide. Dilution with ether and treatment with 10% hydrochloric acid gave three layers. The lower two layers were drawn off and made alkaline with sodium carbonate, and the liberated base was extracted by ether, from which 16 g. of oil was obtained. Repeated attempts to crystallize the compound as the base or as a salt failed, and it was reduced in this crude form. A solution of 37 g. of the crude amino ketone in 300 ml. of 3 *N* aluminum isopropoxide was refluxed for four hours, when the distillate failed to give an acetone test. The product, isolated in the usual way (Procedure 5) and extracted into ether, was isolated as an oil. It was dissolved in acetone and precipitated as a crystalline hydrochloride with ethereal hydrogen chloride; yield 17 g. of m.p. 70–74°; it was recrystallized five times by dissolving in hot acetone and adding dry ether; m.p. 81–83°.

Catalytic reduction of the amino ketone in methanol using platinum oxide proceeded readily, and did not stop after absorption of one molecule of hydrogen. The reaction was interrupted, and on working up the products a very small amount of crystalline hydrochloride was isolated (m.p. 134–135°). Presumably this was a stereoisomer of the product of aluminum isopropoxide reduction, but it was not investigated further.

α-(N-Piperidyl)laurophenone hydrochloride (XXXIXCa). A solution of 20 g. of α-bromolaurophenone in 50 ml. of piperidine, after standing overnight, was filtered from piperidine hydrobromide, diluted with ether, washed with water and dried. Evaporation gave an oil which formed a crystalline hydrochloride from acetone upon addition of ethereal hydrogen chloride; 15 g. (67%); m.p. 119–121°. It was recrystallized four times by dissolving in hot acetone and adding dry ether.

1-Phenyl-2-(N-piperidyl)dodecanol-1 hydrochloride (XXXIXAb). Reduction of 45 g. of the crude amino ketone (base) by 500 ml. of 1.5 *N* aluminum isopropoxide in the usual way (four hours; *cf.* Procedure 5), gave an oil which was converted from acetone into a crystalline hydrochloride (7 g. of m.p. 165–173°); a second crop melting at 95–105° (26 g.) evidently was a mixture of stereoisomers. The first precipitate was repeatedly crystallized from acetone; m.p. 183–187°. The second precipitate, on repeated crystallizations, yielded a considerable amount of additional product of m.p. 183–184°.

Reduction of 4.3 g. of the amino ketone hydrochloride in 350 ml. of absolute ethanol by 15 g. of metallic sodium added over three hours, gave a basic oil which gave a precipitate from acetone upon addition of ethereal hydrogen chloride; 1 g. (23%); m.p. 172–174°. It was purified and shown to be identical with the chief product of the aluminum isopropoxide reduction (m.p. 183–184°).

α-(N-Morpholinyl)laurophenone hydrochloride (*XXXIXCb*) was prepared exactly as was the piperidyl compound. It was recrystallized three times from acetone; m.p. 162–165°.

2-(N-Morpholinyl)-1-phenyldodecanol-1 hydrochloride (*XXXIXAc*) was obtained by aluminum isopropoxide reduction of 50 g. of the crude amino ketone (base) in the same way as the piperidyl analog. The amino alcohol hydrochloride was obtained as two crops, 12 g. of m.p. 167–174° and 29 g. of m.p. 102–105°. The second crop, presumably a mixture of stereoisomers, was not investigated. The first crop was repeatedly crystallized from acetone; m.p. 178–180°.

α-(Dimethylaminomethyl)laurophenone hydrochloride (*XXXIXD*). A suspension of 4.5 g. of dimethylamine hydrochloride, 13 g. of laurophenone and 4.5 g. of paraformaldehyde in 50 ml. of absolute ethanol, acidified with four drops of ethanolic hydrogen chloride, was refluxed for nine days (the reaction had been found in preliminary runs to be exceedingly slow). The mixture was treated with excess ether and hydrochloric acid and the ether layer was evaporated, giving 7.5 g. (43%) of a crystalline hydrochloride of m.p. 107–119°. A small amount of the same compound crystallized from the aqueous layer (0.1 g.). Repeated crystallizations from acetone by addition of dry ether gave a pure product of m.p. 129–129.5°.

2-(Diethylaminomethyl)-1-phenyldodecanol-1 hydrochloride (*XXXIXB*). Many experiments were carried out before the desired amount of ketone could be obtained in significant yield; it could not be obtained as a crystalline hydrochloride under the usual conditions and was consequently reduced without purification.

A solution of 52 g. of laurophenone, 30 g. of diethylamine hydrochloride, and 20 g. of paraformaldehyde in 200 ml. of absolute ethanol and 4 ml. of concentrated ethanolic hydrogen chloride was refluxed for ten days with addition, at intervals, of a total of 34 g. of additional paraformaldehyde. Evaporation of the ethanol and treatment with dilute hydrochloric acid and ether produced three layers, the middle layer consisting of the oily amino ketone hydrochloride. From the ether layer 13 g. of laurophenone was recovered. Treatment of the two lower layers with sodium carbonate and extraction with ether gave 41 g. of crude amino ketone.

A solution of 7 g. of the crude amino ketone in 300 ml. of 0.75 *N* aluminum isopropoxide was refluxed for six hours, when acetone could no longer be detected in the distillate. The product was isolated as an oil which was converted in the usual way into a hydrochloride (from acetone with ethereal hydrogen chloride); yield 1 g. (8% calculated from laurophenone); m.p. after two crystallizations from acetone, 154–155°. It was soluble in water.

XXXX. 3-BROMO-4-CHLOROACETOPHENONE AND 3-IODO-4-CHLOROACETOPHENONE

The preparation of the 3-bromo-4-chloro and 3-iodo-4-chloro series of dialkylaminoethanols was begun but was discontinued in favor of more pressing problems.

4-Chloroacetophenone was chosen as starting material, and was nitrated, reduced, diazotized, and then converted into the 3-bromo-4-chloro-and 3-iodo-4-chloro-acetophenones by treatment with cuprous bromide and potassium iodide, respectively. The structures of these two new acetophenones were verified by oxidation to the known dihalogenobenzoic acids.

EXPERIMENTAL[6]

4-Chloro-3-nitroacetophenone (86, 87) was best obtained using mixed nitric and sulfuric acids (87) at a temperature of −5°, and the detailed procedure of Morgan and Watson (88) for the nitration of acetophenone itself; white crystals; yield after recrystallizing from dilute acetic acid, 83%; m.p. 97–99° [Le F. and Le F. (86), 99–101°] [M., S., and S. (87), yellow crystals, 77%, 104°].

A lower nitration temperature than −5° gave only a partial conversion of starting material into the nitro compound (29% at −30°, and 38% at −15°). The use of a less drastic nitrating mixture (nitric acid alone at 5° or a sulfuric acid solution of sodium nitrate at 15°) resulted only in the recovery of starting material. When more drastic conditions were tried, little or none of the desired product was obtained; carrying out the nitration at 10° gave only a 5% yield; the use of nitric acid at room temperature or a sulfuric acid solution of sodium nitrate at 40° gave products (m.p. 114–117° and oil, respectively) which were not investigated further.

3-Amino-4-chloroacetophenone was prepared by adding 10 g. of 4-chloro-3-nitroacetophenone to 45 ml. of concentrated hydrochloric acid containing 34 g. of stannous chloride dihydrate; the hydrochloride precipitated and was converted to the free base by alkali; colorless crystals, m.p. 105–107°; yield 7 g. (82%).

Anal. Calc'd for C_8H_8ClNO: N, 8.26. Found: N, 8.11.

3-Bromo-4-chloroacetophenone was prepared by suspending 5.1 g. (0.03 mole) of 3-amino-4-chloroacetophenone in a mixture of 25 ml. of 40% hydrobromic acid and 10 ml. of water under mechanical stirring, cooling in an ice-salt bath, slowly adding an excess of sodium nitrite solution, destroying the excess a few minutes later with urea, allowing the mixture to stir for another hour, and then pouring it into a warm solution which consisted of 0.03 mole of freshly prepared cuprous bromide dissolved in 40% hydrobromic acid. The product was filtered and recrystallized from 50% ethanol; light orange solid; m.p. 80–82°; yield 4.8 g. (68%). A pure sample was obtained by vacuum sublimation, white crystals, m.p. 85.5°.

Anal. Calc'd for C_8H_6BrClO: C, 41.15; H, 2.59.
Found: C, 41.39; H, 2.73.

Oxidation with alkaline permanganate gave *3-bromo-4-chlorobenzoic acid* in 70% yield, m.p. 217–219° [H. & B. (89), 215–216°].

4-Chloro-3-iodoacetophenone was prepared by adding 50 g. of 4-chloro-3-nitroacetophenone to 225 ml. of concentrated hydrochloric acid containing 170 g. of stannous chloride dihydrate, diluting with 500 ml. of glacial acetic acid (after the reaction subsided), cooling to −1° in an ice-salt bath, adding 46.5 g. (0.67 mole) of sodium nitrite in 70 ml. of water over a period of two and one-half hours, stirring for an additional two hours, adding 40 g. (0.67 mole) of urea in 100 ml. of water during one hour, adding 41 g. (0.25 mole) of potassium iodide in 200 ml. of water, allowing the cooled mixture to stir overnight, warming it on a water-bath for thirty minutes, diluting with water, again cooling, filtering, and recrystallizing from 95% ethanol; the yield was 18 g. (26%); light orange crystals; m.p. 84–86°.

Anal. Calc'd for C_8H_6ClIO: C, 34.25; H, 2.16.
Found: C, 34.39; H, 2.30.

Oxidation with alkaline permanganate gave *4-chloro-3-iodobenzoic acid* in almost quantitative yield; m.p. 217–219° [H. & B. (89), 216–217°].

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TABLE II. ANALYSES

COMPOUND NO.	EMPIRICAL FORMULA	C (or N or Cl^-)		H	
		CALC'D	FOUND	CALC'D	FOUND
IA a	$C_{24}H_{43}NO$	$^{N}3.87$	4.15	—	—
b	$C_{26}H_{47}NO$	$^{N}3.59$	3.79	—	—
c	$C_{16}H_{19}NO$	$^{N}5.81$	6.04	—	—
d	$C_{16}H_{18}ClNO$	$^{N}5.11$	4.99	—	—
e	$C_{16}H_{18}ClNO$	$^{N}5.11$	5.40	—	—
f	$C_{22}H_{23}NO\cdot HCl$	74.66	74.60	6.84	6.81[a]
IIA a	$C_{12}H_{16}ClNO$	$^{N}6.15$	6.03	—	—
b	$C_{16}H_{26}ClNO$	$^{N}4.94$	4.79	—	—
b_1	$C_{16}H_{26}ClNO\cdot HCl$	59.99	59.82	8.50	8.32
c	$C_{16}H_{26}ClNO$	67.70	67.34	9.23	9.38
d	$C_{18}H_{30}ClNO$	69.32	69.39	9.70	9.68[a]
e	$C_{18}H_{30}ClNO$	$^{N}4.49$	4.49	—	—
f	$C_{20}H_{34}ClNO$	70.66	70.55	10.08	10.38
g	$C_{22}H_{38}ClNO\cdot HCl$	$^{N}3.46$	3.57	—	—
h	$C_{24}H_{42}ClNO$	72.78	72.43	10.69	10.85
h_1	$C_{24}H_{42}ClNO\cdot HCl$	$^{Cl^-}8.20$	8.29	—	—
i	$C_{24}H_{42}ClNO$	72.78	72.43	10.69	10.93[a]
j	$C_{26}H_{46}ClNO$	73.63	73.96	10.93	11.28
k	$C_{28}H_{50}ClNO$	74.37	74.73	11.15	11.48[a]
l	$C_{30}H_{54}ClNO$	$^{N}2.92$	3.23	—	—
l_1	$C_{30}H_{54}ClNO\cdot HCl$	$^{Cl^-}6.86$	6.69	—	—
m	$C_{32}H_{58}ClNO$	$^{N}2.76$	2.90	—	—
n	$C_{34}H_{62}ClNO$	$^{N}2.61$	2.85	—	—
o	$C_{16}H_{18}ClNO\cdot HCl$	$^{Cl^-}11.36$	11.73	—	—
p	$C_{17}H_{20}ClNO$	$^{N}4.83$	4.66	—	—
q	$C_{18}H_{22}ClNO$	71.15	71.23	7.30	7.14
r	$C_{18}H_{22}ClNO$	$^{N}4.61$	4.85	—	—
r_1	$C_{18}H_{22}ClNO\cdot HCl$	63.53	63.46	6.81	6.80
s	$C_{19}H_{24}ClNO$	71.79	71.61	7.61	7.44
t	$C_{19}H_{24}ClNO\cdot HCl$	64.40	64.82	7.11	6.85[a]
u	$C_{20}H_{26}ClNO$	$^{N}4.22$	4.42	—	—
v	$C_{27}H_{40}ClNO$	75.40	75.35	9.38	9.51[a]
w	$C_{21}H_{26}ClNO\cdot HCl$	$^{N}3.68$	3.99	—	—
x	$C_{20}H_{26}ClNO$	$^{N}4.22$	4.37	—	—
y	$C_{16}H_{17}Cl_2NO\cdot HCl$	$^{N}4.05$	3.79	—	—
z	$C_{17}H_{20}ClNO_2\cdot HCl$	$^{N}4.10$	4.00	—	—
aa	$C_{20}H_{26}ClNO_2$	$^{N}4.03$	4.17	—	—
bb	$C_{22}H_{22}ClNO$	75.09	75.00	6.30	6.60
bb_1	$C_{22}H_{22}ClNO\cdot HCl$	$^{Cl^-}9.13$	9.23		
cc	$C_{15}H_{18}ClNO_2$	$^{N}5.00$	4.75	—	—
dd	$C_{20}H_{20}ClNO\cdot HCl$	66.30	66.04	5.84	5.80[a]
ee	$C_{22}H_{31}ClN_2O$	70.46	70.35	8.34	9.47
ff	$C_{26}H_{39}ClN_2O$	72.44	72.61	9.12	9.47
gg	$C_{17}H_{18}ClNO$	$^{N}4.87$	4.66	—	—
gg_1	$C_{17}H_{18}ClNO\cdot HCl$	62.97	62.50	5.91	6.37[a]

TABLE II—*Continued*

COMPOUND NO.	EMPIRICAL FORMULA	C (OR N OR Cl⁻)		H	
		CALC'D	FOUND	CALC'D	FOUND
hh	$C_{17}H_{18}ClNO$	N 4.87	4.64	—	—
ii	$C_{12}H_{16}ClNO_2$	N 5.80	5.38	—	—
jj	$C_{13}H_{18}ClNO_2$	N 5.48	5.19	—	—
kk	$C_{14}H_{20}ClNO_2$	N 5.19	4.89	—	—
ll	$C_{19}H_{30}ClNO$	N 4.32	4.62	—	—
mm	$C_{20}H_{28}ClNO$	71.94	71.75	8.45	8.31[a]
nn	$C_{18}H_{22}ClNO \cdot HCl$	63.54	63.46	6.52	6.83[a]
IIB a	$C_{12}H_{16}ClNO \cdot HCl$	N 5.34	5.44	—	—
b	$C_{16}H_{16}ClNO \cdot HCl$	N 4.52	4.25	—	—
c	$C_{19}H_{22}ClNO \cdot HCl$	N 3.98	4.09	—	—
e	$C_{21}H_{24}ClNO \cdot HCl$	N 3.70	3.88	—	—
f	$C_{20}H_{18}ClNO \cdot HCl$	N 3.89	3.80	—	—
g	$C_{17}H_{16}ClNO$	N 4.90	4.96	—	—
h_1	$C_{12}H_{14}ClNO_2 \cdot HCl$	N 5.07	5.16	—	—
i	$C_{13}H_{16}ClNO_2 \cdot HCl$	N 4.83	5.19	—	—
j	$C_{14}H_{18}ClNO_2 \cdot HCl$	N 4.61	4.80	—	—
m	$C_{21}H_{18}ClNO \cdot HCl$	67.74	68.08	5.14	5.08
n	$C_{17}H_{16}ClNO$	N 4.90	4.98	—	—
IIC a	$C_{19}H_{30}ClNO \cdot HCl$	63.32	63.62	8.67	8.35
b	$C_{17}H_{18}ClNO \cdot HCl$	N 4.32	N 4.55	—	—
IIIA a	$C_{16}H_{26}BrNO \cdot HCl$	52.68	52.92	7.46	7.20[a]
b	$C_{18}H_{20}BrNO$	N 3.93	4.02	—	—
c	$C_{18}H_{30}BrNO$	N 3.93	4.01	—	—
d	$C_{20}H_{34}BrNO$	N 3.64	4.04	—	—
e	$C_{22}H_{38}BrNO \cdot HCl$	N 3.12	2.87	—	—
f	$C_{24}H_{42}BrNO$	N 3.18	3.16	—	—
g	$C_{26}H_{46}BrNO$	N 3.00	3.02	—	—
h	$C_{16}H_{18}BrNO \cdot HCl$	53.87	53.58	5.37	5.42[a]
i	$C_{19}H_{24}BrNO \cdot HCl$	Cl^- 8.90	9.02	—	—
j	$C_{12}H_{16}BrNO_2$	50.35	50.24	5.64	5.61[a]
k	$C_{13}H_{18}BrNO_2$	N 4.67	N 4.99	—	—
l	$C_{14}H_{20}BrNO_2 \cdot HCl$	47.94	47.72	6.04	5.47[a]
m	$C_{14}H_{20}BrNO_2 \cdot HCl$	N 4.00	4.08	—	—
n	$C_{14}H_{20}BrNO_2 \cdot HCl$	N 4.00	4.29	—	—
o	$C_{14}H_{20}BrNO_2 \cdot HCl$	N 4.00	3.87	—	—
p	$C_{17}H_{24}BrNO \cdot HCl$	N 3.74	3.92	—	—
q	$C_{15}H_{16}BrNO$	N 4.58	4.51	—	—
IIIB	$C_{15}H_{24}BrNO \cdot HCl$	N 3.99	4.04	—	—
IIIC b	$C_{16}H_{16}BrNO \cdot HCl$	N 3.95	3.97	—	—
c	$C_{19}H_{22}BrNO \cdot HCl$	Cl^- 8.94	8.80	—	—
d_1	$C_{12}H_{14}BrNO_2 \cdot HCl$	N 4.37	4.22	—	—
e	$C_{13}H_{16}BrNO_2 \cdot HCl$	46.66	46.30	5.12	5.05[a]
f	$C_{14}H_{18}BrNO_2 \cdot HCl$	48.22	47.88	5.49	5.49[a]

TABLE II—*Continued*

COMPOUND NO.	EMPIRICAL FORMULA	C (OR N OR Cl⁻)		H	
		CALC'D	FOUND	CALC'D	FOUND
g	$C_{14}H_{18}BrNO_2 \cdot HCl$	$^{N}4.02$	4.24	—	—
h_1	$C_{14}H_{18}BrNO_2 \cdot HCl$	$^{N}4.02$	3.91	—	—
i	$C_{17}H_{22}BrNO$	60.72	60.78	6.60	6.25
j	$C_{15}H_{14}BrNO$	$^{N}4.61$	4.48	—	—
IIID a	$C_{15}H_{22}BrNO \cdot HCl$	$^{Cl^-}10.17$	10.22	—	—
b	$C_{17}H_{26}BrNO \cdot HCl$	$^{N}3.72$	4.00	—	—
IVA a	$C_{12}H_{18}INO \cdot HCl$	$^{Cl^-}9.97$	10.01	—	—
b	$C_{14}H_{22}INO \cdot HCl$	$^{Cl^-}9.24$	9.41	—	—
c	$C_{16}H_{26}INO \cdot HCl$	$^{N}3.40$	3.31	—	—
d	$C_{12}H_{18}INO \cdot HCl$	$^{N}3.94$	3.65	—	—
e	$C_{18}H_{30}INO \cdot HCl$	49.15	49.34	7.11	7.43
f_1	$C_{24}H_{42}INO \cdot HCl$	$^{N}2.67$	$^{N}2.70$	—	—
g	$C_{16}H_{18}INO \cdot HCl$	$^{N}3.47$	3.76	—	—
h	$C_{13}H_{18}INO \cdot HCl$	$^{Cl^-}9.65$	9.76	—	—
IVB a	$C_{14}H_{20}INO \cdot HCl$	$^{N}3.67$	3.63	—	—
b	$C_{16}H_{24}INO \cdot HCl$	$^{N}3.42$	3.38	—	—
c	$C_{16}H_{16}INO \cdot HCl$	$^{N}3.49$	3.26	—	—
d	$C_{13}H_{16}INO \cdot HCl$	$^{N}3.83$	3.78	—	—
V a	$C_{24}H_{42}FNO$	75.93	75.43	11.15	11.15
b	$C_{26}H_{46}FNO$	76.60	76.47	11.37	11.18
c	$C_{19}H_{24}FNO$	75.71	75.36	8.03	8.15
VI a	$C_{24}H_{42}ClNO$	$^{N}3.54$	3.46	—	—
b	$C_{16}H_{18}ClNO \cdot HCl$	$^{N}4.49$	4.66	$^{Cl^-}11.36$	11.59
VII a_1	$C_{13}H_{20}ClNO \cdot HCl$	$^{N}4.02$	3.68	—	—
b	$C_{24}H_{42}ClNO$	$^{N}3.54$	3.62	—	—
c_1	$C_{16}H_{18}ClNO \cdot HCl$	61.54	61.52	6.13	6.15[a]
VIIIA a	$C_{16}H_{26}BrNO \cdot HCl$	$^{N}3.84$	4.08	—	—
b	$C_{18}H_{30}BrNO$	60.67	61.39	8.49	8.88[a]
c	$C_{16}H_{18}BrNO \cdot HCl$	53.87	53.98	5.37	5.20[a]
VIIIB	$C_{16}H_{16}BrNO \cdot HCl$	$^{N}3.95$	3.94	—	—
IX	$C_{16}H_{18}BrNO$	$^{N}4.37$	4.62	—	—
XA a	$C_{10}H_{14}INO$	$^{N}4.81$	4.65	—	—
b_1	$C_{12}H_{18}INO \cdot HCl$	$^{N}3.94$	4.18	—	—
c_1	$C_{14}H_{22}INO \cdot HCl$	$^{Cl^-}9.24$	9.32	—	—
d_1	$C_{16}H_{26}INO \cdot HCl$	46.67	46.39	6.61	6.68
e_1	$C_{16}H_{18}INO \cdot HCl$	$^{Cl^-}8.78$	8.90	—	—
XB	$C_{16}H_{16}INO \cdot HCl$	47.84	48.20	4.27	4.59

TABLE II—*Continued*

COMPOUND NO.	EMPIRICAL FORMULA	C (OR N OR Cl^-)		H	
		CALC'D	FOUND	CALC'D	FOUND
XI a	$C_{12}H_{18}INO \cdot HCl$	Cl^-9.97	10.2	—	—
b	$C_{14}H_{22}INO \cdot HCl$	43.82	44.02	6.04	5.92
c	$C_{16}H_{26}INO \cdot HCl$	Cl^-8.61	8.70	—	—
d	$C_{16}H_{18}INO \cdot HCl$	N3.47	3.23	—	—
XII a	$C_{19}H_{33}NO_2$	74.22	73.88	10.82	10.61
b	$C_{20}H_{35}NO_2$	74.71	73.79	10.97	10.70
c	$C_{20}H_{35}NO_2$	74.71	74.71	10.97	10.93
XIII a	$C_{19}H_{33}NO$	78.29	78.35	11.41	11.40
b	$C_{21}H_{37}NO$	78.94	79.14	11.67	11.75
c	$C_{24}H_{43}NO$	N3.87	3.68	—	—
d	$C_{30}H_{55}NO$	N3.14	3.24	—	—
e	$C_{18}H_{29}NO$	78.49	78.58	10.61	11.03
f	$C_{22}H_{37}NO$	79.70	79.81	11.25	11.40
g	$C_{26}H_{47}NO$	N3.59	3.81	—	—
h	$C_{24}H_{43}NO$	N3.87	2.89	—	—
XIVA	$C_{22}H_{32}NO$	N4.13	3.88	—	—
XIVB	$C_{20}H_{25}NO \cdot HCl$	Cl^-10.68	11.12	—	—
XVA	$C_{24}H_{35}NO \cdot HCl$	73.91	73.76	9.31	9.11[a]
XVB	$C_{20}H_{23}NO_2$	77.64	77.31	7.49	7.33
XVIA a	$C_{19}H_{32}ClNO$	70.02	70.08	9.90	10.03
b	$C_{25}H_{44}ClNO$	N3.42	3.47	—	—
c	$C_{17}H_{20}ClNO \cdot HCl$	N4.29	4.51	X21.74	21.46
XVIB	$C_{17}H_{18}ClNO \cdot HCl$	63.00	63.12	5.91	5.86[a]
XVIIA a	$C_{19}H_{32}ClNO$	N4.30	4.52	—	—
b	$C_{25}H_{44}ClNO$	N3.42	3.50	—	—
c	$C_{17}H_{20}ClNO \cdot HCl$	N4.29	4.12	—	—
XVIIB	$C_{17}H_{18}ClNO \cdot HCl$	N4.31	4.27		
XVIII a	$C_{19}H_{32}ClNO$	N4.30	4.24	—	—
b	$C_{17}H_{20}ClNO$	N4.83	4.77	—	—
XIX a	$C_{25}H_{44}ClNO$	N3.42	3.34	—	—
b	$C_{17}H_{20}ClNO \cdot HCl$	N4.29	4.20	Cl^-10.87	10.91
XXA a	$C_{14}H_{22}ClNO_2 \cdot HCl$	N4.54	4.27	—	—
b	$C_{20}H_{34}ClNO_2 \cdot HCl$	N3.57	3.28	—	—
c	$C_{18}H_{22}ClNO_2 \cdot HCl$	60.68	60.46	6.51	6.80[a]
d	$C_{19}H_{24}ClNO_2 \cdot HCl$	N3.78	3.95	—	—
XXB	$C_{18}H_{20}ClNO_2 \cdot HCl$	N3.95	4.12	—	—

TABLE II—*Continued*

COMPOUND NO.	EMPIRICAL FORMULA	C (OR N OR Cl⁻)		H	
		CALC'D	FOUND	CALC'D	FOUND
XXI	$C_{19}H_{32}ClNO_2 \cdot HCl$	60.30	60.59	8.79	8.66
XXII a	$C_{17}H_{28}BrNO$	$^{N}4.09$	4.24	—	—
b	$C_{19}H_{32}BrNO$	61.61	62.00	8.71	8.98
c	$C_{25}H_{44}BrNO$	$^{N}3.08$	3.20	—	—
d	$C_{17}H_{20}BrNO$	$^{N}4.19$	3.89	—	—
XXIII	$C_{19}H_{32}BrNO$	$^{N}3.78$	3.97	—	—
XXIV a	$C_{17}H_{28}BrNO \cdot HCl$	53.90	53.89	7.72	7.69
b	$C_{25}H_{44}BrNO$	66.06	66.05	9.76	9.56[a]
XXVA a	$C_{12}H_{17}Cl_2NO \cdot HCl$	$^{Cl^-}11.87$	11.98	—	—
a_1	$C_{18}H_{20}Cl_2N_4O_8$	$^{N}11.41$	11.28	—	—
b	$C_{16}H_{25}Cl_2NO$	60.37	60.03	7.92	7.82
c	$C_{18}H_{29}Cl_2NO$	$^{N}4.05$	4.42	—	—
d	$C_{24}H_{41}Cl_2NO$	$^{N}3.25$	3.39	—	—
e	$C_{16}H_{17}Cl_2NO \cdot HCl$	55.43	55.42	5.24	5.42
f	$C_{22}H_{21}Cl_2NO \cdot HCl$	$^{N}3.33$	3.35	—	—
g	$C_{17}H_{19}Cl_2NO \cdot HCl$	$^{N}3.88$	3.76	—	—
h	$C_{16}H_{25}Cl_2NO \cdot HCl$	$^{N}3.95$	3.98	$^{Cl^-}10.00$	10.13
i	$C_{20}H_{29}Cl_2NO \cdot HCl$	$^{N}3.44$	3.53	—	—
XXVB	$C_{22}H_{19}Cl_2NO \cdot HCl$	$^{N}3.33$	3.46	—	—
XXVI a	$C_{16}H_{25}Cl_2NO \cdot HCl$	$^{N}3.95$	4.19	—	—
b	$C_{24}H_{41}Cl_2NO_2 \cdot HCl$	61.73	61.85	9.07	8.80[a]
XXVII a	$C_{24}H_{41}Cl_2NO \cdot HCl$	$^{N}3.00$	3.28	$^{Cl^-}7.59$	7.37
b	$C_{16}H_{17}Cl_2NO$	$^{N}4.52$	4.89	—	—
XXVIII a	$C_{16}H_{25}Cl_2NO \cdot HCl$	54.17	54.15	7.39	7.35
b	$C_{16}H_{17}Cl_2NO \cdot HCl$	55.43	55.66	5.23	5.10[a]
XXIX	$C_{24}H_{41}Cl_2NO \cdot HCl$	61.73	61.40	9.07	8.87[a]
XXXA a	$C_{12}H_{17}Br_2NO \cdot HCl$	37.19	37.30	4.68	4.70[a]
b	$C_{18}H_{29}Br_2NO \cdot HCl$	$^{N}2.97$	2.83	$^{Cl^-}7.52$	7.68
c	$C_{16}H_{17}Br_2NO$	$^{N}3.51$	3.78	—	—
XXXB	$C_{16}H_{16}Br_2NO \cdot HCl$	$^{Cl^-}8.18$	8.09	—	—
XXXIA	$C_{18}H_{31}NO$	$^{N}5.05$	4.85	—	—
XXXIB	$C_{18}H_{27}NO_2 \cdot HCl$	$^{Cl^-}10.88$	10.80	—	—

TABLE II—*Continued*

COMPOUND NO.	EMPIRICAL FORMULA	C (OR N OR Cl⁻)		H	
		CALC'D	FOUND	CALC'D	FOUND
XXXIIIA a	$C_{16}H_{27}NO$	77.05	76.69	10.91	10.43
b	$C_{20}H_{35}NO\cdot HCl$	$^{N}4.10$	4.15	$^{Cl^-}10.37$	10.44
c	$C_{17}H_{27}NO\cdot HCl$	68.55	68.32	9.48	9.38[a]
d	$C_{16}H_{25}NO_2\cdot HCl$	64.09	63.68	8.74	8.44
e	$C_{19}H_{32}NO$	$^{N}4.81$	4.92	—	—
XXXIIIB a	$C_{17}H_{25}NO\cdot HCl$	69.01	68.71	8.86	9.01[a]
b	$C_{16}H_{23}NO_2\cdot HCl$	64.52	64.49	8.12	7.82[a]
XXXIII a	$C_{17}H_{27}Cl_2NO$	$^{X}21.34$	21.24	—	—
b	$C_{19}H_{31}Cl_2NO$	$^{X}19.68$	19.53	—	—
c	$C_{25}H_{43}Cl_2NO\cdot HCl$	62.42	62.84	9.22	8.90[a]
d	$C_{17}H_{19}Cl_2NO\cdot HCl$	56.65	56.89	5.31	5.78[a]
XXXIV a	$C_{17}H_{27}Cl_2NO$	$^{N}4.22$	4.42	—	—
b	$C_{19}H_{31}Cl_2NO$	$^{X}19.68$	19.70	—	—
c	$C_{25}H_{43}Cl_2NO$	$^{X}15.96$	15.82	—	—
c_1	$C_{25}H_{43}Cl_2NO\cdot HCl$	62.42	61.95	9.22	9.10[a]
XXXVA a	$C_{19}H_{32}ClNO$	$^{N}4.30$	4.01	—	—
b	$C_{25}H_{44}ClNO$	$^{N}3.42$	3.68	—	—
c	$C_{17}H_{20}ClNO$	70.45	70.14	6.96	6.90[a]
d	$C_{14}H_{20}ClNO\cdot HCl$	$^{N}4.83$	4.63	$^{Cl^-}12.22$	12.31
e	$C_{18}H_{30}ClNO$	69.31	69.80	9.70	10.23
f	$C_{20}H_{34}ClNO$	70.66	70.98	10.08	10.40
g	$C_{20}H_{34}ClNO$	70.66	71.02	10.08	10.32
h	$C_{20}H_{26}ClNO$	72.38	72.48	7.90	7.93
i	$C_{17}H_{26}ClNO$	$^{N}4.74$	4.92	—	—
i_1	$C_{17}H_{26}ClNO\cdot HCl$	$^{Cl^-}10.67$	10.51	—	—
j	$C_{21}H_{26}ClNO\cdot HCl$	$^{N}3.68$	3.91	—	—
XXXVB a	$C_{17}H_{18}ClNO\cdot HCl$	$^{N}4.32$	3.96	—	—
b	$C_{14}H_{18}ClNO$	$^{N}5.56$	5.47	—	—
b_1	$C_{14}H_{18}ClNO\cdot HCl$	$^{N}4.86$	5.09	—	—
c	$C_{20}H_{24}ClNO\cdot HCl$	$^{N}3.82$	4.06	—	—
d	$C_{17}H_{24}ClNO\cdot HCl$	$^{N}4.24$	3.86	—	—
e	$C_{21}H_{24}ClNO\cdot HCl$	$^{N}3.70$	3.44	—	—
XXXVI b	$C_{19}H_{32}BrNO$	$^{N}3.78$	3.69	—	—
XXXVII	$C_{18}H_{22}BrNO$	$^{N}4.02$	3.97	—	—
XXXVIIIA a	$C_{20}H_{35}NO$	78.63	78.28	11.55	11.45
b	$C_{17}H_{27}NO$	78.11	78.43	10.41	9.96
c	$C_{16}H_{25}NO_2\cdot HCl$	64.09	64.07	8.74	8.78
d	$C_{23}H_{39}NO$	$^{N}4.20$	4.09	—	—
e	$C_{19}H_{33}NO$	$^{N}4.81$	4.42	—	—
f	$C_{20}H_{35}NO\cdot HCl$	$^{Cl^-}10.37$	10.63	—	—

TABLE II—*Concluded*

COMPOUND NO.	EMPIRICAC FORMULA	C (OR N OR Cl^-)		H	
		CALC'D	FOUND	CALC'D	FOUND
XXXVIIIB a	$C_{17}H_{25}NO \cdot HCl$	69.01	68.88	8.86	8.72
b	$C_{16}H_{23}NO_2 \cdot HCl$	64.51	64.85	8.12	8.62[a]
XXXIXA a	$C_{22}H_{29}NO \cdot HCl$	71.41	71.48	10.90	10.75
b	$C_{23}H_{29}NO \cdot HCl$	72.31	72.59	10.55	10.65
c	$C_{22}H_{27}NO_2 \cdot HCl$	68.81	68.81	9.98	9.78
XXXIXB	$C_{23}H_{41}NO \cdot HCl$	71.93	72.19	11.02	11.35
XXXIXC a	$C_{23}H_{37}NO \cdot HCl$	72.69	72.51	10.08	10.28
b	$C_{22}H_{35}NO_2 \cdot HCl$	69.17	68.76	9.50	9.67
XXXIXD	$C_{21}H_{35}NO \cdot HCl$	71.25	71.41	10.25	10.50

[a] Additional Analyses.

FORMULA NO.	CALC'D N	FOUND N	FORMULA NO.	CALC'D N	FOUND N	FORMULA NO.	CALC'D N	FOUND N
IA f	3.96	4.03	j	4.90	4.76	XXIX	3.00	3.11
IIA d	4.49	4.61	l	4.00	4.03		Cl^-7.59	7.56
i	3.54	3.33	IIIC e	4.19	4.07	XXXA a	3.62	3.86
k	3.10	3.23	f	4.02	3.95	XXXIIA c	Cl^-11.91	11.90
t	3.95	4.35	$VIIC_1$	Cl^-11.35	11.50	XXXIIB a	4.74	4.22
v	3.26	3.58	VIIIA b	3.93	4.43	b	4.70	4.54
dd	3.87	4.06	c	Cl^-9.94	10.19		Cl^-11.91	11.84
gg_1	Cl^-10.93	11.18	XVA	Cl^-9.09	9.13	XXXIII c	Cl^-7.37	7.46
mm	4.20	4.49	XVIB	4.32	4.23	d	Cl^-9.83	9.84
nn	4.12	4.39	XXA c	3.93	4.10	XXXIV c_1	2.91	3.19
			XXIV b	3.08	3.28			
IIIA a	3.84	3.93	XXVI b	3.00	3.07		Cl^-7.37	7.62
	Cl^-9.72	9.83		Cl^-7.59	7.71	XXXVA c	4.83	4.65
h	3.93	3.85	XXVIII b	4.04	4.34	XXXVIIIB b	4.72	4.67

[N] These analyses are for nitrogen rather than carbon and hydrogen.

[Cl^-] These analyses are for chloride ion (titration method).

[X] These figures represent the total chlorine content, and were carried out by Miss Elizabeth Wilson, using the nickel-aluminum alloy reduction method (91).

SUMMARY

The discovery of moderate antimalarial activity in the nuclear substituted α-phenyl-β-dialkylaminoethanols led to an extensive investigation designed to evaluate the effect of: (a) the phenyl nucleus itself, (b) variation in the alkyl groups on nitrogen, (c) substitution of halogen in the phenyl nucleus, (d) substitution of other groups including alkyl and alkoxyl, (e) the location of the substituent in the nucleus, (f) substitution of two or more groups in different nuclear positions, (g) lengthening the amino alcohol chain to three, four, six,

and twelve carbons, and (h) the separation of the alcoholic hydroxyl and the *tert.*-amino group by three carbons instead of two.

A total of 184 amino alcohols and 55 amino ketones were synthesized and submitted for screening tests against avian malaria. These compounds included examples of fifty variations in the phenyl nucleus and over sixty variations in the N,N-dialkyl groups on the nitrogen. A large number of N-alkyl-N-benzyl-amino types were made.

Most of the drugs were made by condensation of the α-bromoacetophenone and the appropriate secondary amine to give the *tert.*-amino ketones, and by reduction of these with aluminum isopropoxide. The alternative path used in a few cases was the reduction of the α-bromoacetophenone to the bromohydrin and condensation directly with the secondary amine.

Most of the bromomethyl ketones which were not available were made by bromination of the appropriate acetophenone; a few were made from the acids through the acid chlorides by diazomethylation and treatment with hydrobromic acid. Some of the methyl ketones were made by the Friedel-Crafts reaction on the appropriate benzene derivative; and in two cases chloromethyl ketones were made by this reaction. A few methyl ketones were made by addition of methylmagnesium iodide to the appropriate nitrile, and one was made by oxidation of the secondary alcohol which had been obtained from the aldehyde by addition of methylmagnesium iodide.

Two drugs were prepared both through the bromohydrin (the more convenient path) and through the amino ketone. The latter synthesis demonstrated the mode of the ethylene oxide ring cleavage involved.

In the distillation of the amino alcohols of high molecular weight hydramine fission often occurred to some extent. Also in some cases the partial displacement of ortho or para halogen was noted.

The following *mono-substituents* were introduced into the nucleus of the α-phenyl-β-dialkylaminoethanols: 4-chloro, 4-bromo, 4-iodo, 4-fluoro, 3-chloro, 2-chloro, 3-bromo, 2-bromo, 3-iodo, 2-iodo, 4-methoxy, 4-ethoxy, 4-(*n*-butoxy), 4-isopropyl, 4-*n*-hexyl, 4-cyclohexyl, 4-*n*-decyl, 4-*n*-dodecyl, 4-benzyl, and 4-(β-phenylethyl).

The following *di-substitutions* were made: 4-chloro-3-methyl, 3-chloro-4-methyl, 2-chloro-4-methyl, 2-chloro-5-methyl, 3-chloro-6-methoxy, 3-chloro-4-ethoxy, 4-bromo-3-methyl, 4-bromo-2-methyl, 3-bromo-4-methyl, 3,4-dichloro, 2,4-dichloro, 2,5-dichloro, 3,5-dichloro, 2,6-dichloro, 3,5-dibromo, 2,4-di-(isopropyl), and 5-isopropyl-2-methyl.

The following *tri-substitutions* were made: 2,4-dichloro-3-methyl and 3,4-dichloro-6-methyl.

α-4-Chlorophenyl-β-dialkylamino alcohols were made with amino alcohol chains of 3, 4, and 6 carbons; also α-4-bromophenyl analogs of the first of these types. In the α-phenyl-β-dialkylaminohexanols, the following substituents were employed: none, 4-ethyl, 4-isopropyl, and 4-*tert.*-butyl. The series of α-phenyl-β-dialkylaminododecanols carried no nuclear substituents.

In the α-4-chlorophenyl-β-aminoethanol series the following dialkyl substitu-

tions on the nitrogen were employed: diethyl, di-*n*-butyl, di-isobutyl, diamyl, di-isoamyl, dihexyl, diheptyl, dioctyl, di-(2-ethylhexyl), dinonyl, didecyl, diundecyl, didodecyl, and ditridecyl. The following N-alkyl-N-benzyl groups were employed: benzylmethyl, benzylethyl, benzylpropyl, benzylisopropyl, benzylbutyl, benzyl-(2-methylpropyl), benzylamyl, benzyloctyl, benzyldodecyl, benzylcyclohexyl, (α-butylbenzyl)methyl, 4-chlorobenzylmethyl, 4-methoxybenzylmethyl, 4-methoxybenzylbutyl, and dibenzyl; also the following analogous types: (α-furylmethyl)ethyl, (α-naphthylmethyl)methyl, benzyl(3-diethylaminopropyl), benzyl(3-dibutylaminopropyl), and N-tetrahydroisoquinolyl. The following miscellaneous groupings were used: morpholinyl, 2-methylmorpholinyl, 2,6-dimethylmorpholinyl, 2-(*n*-hexyl) piperidyl, *trans*-dodecahydrocarbazyl, N-methyl-N-phenyl, N-butyl-N-phenyl, benzylphenyl, and tetrahydroquinolyl.

In certain series other than the 4-chlorophenyl the following $-NR_2$ groups, in addition to the above, were employed: monooctyl, 2-chlorobenzylmethyl, 2-ethylmorpholinyl, 3-ethylmorpholinyl, and 3,3-dimethylmorpholinyl.

Representative β-*tert.*-amino ketones were made by the Mannich reaction on the following: 4-chloro- and 4-bromoacetophenones, and laurophenone.

The following γ-*tert.*-amino alcohols were made by reduction of the β-*tert.*-amino ketones: α-(4-bromophenyl)-γ-dialkylaminopropanol, and α-phenyl-β-dialkylaminomethylhexanol.

The antimalarial activities of the majority of these drugs ranged from Q = 0.1 to Q = 0.5 and in a few cases reached Q = 1 against *gallinaceum* in the chick, and in one case Q = 2 against *lophurae* in the duck. The highest activities were found in the following types: 2,4-dichloro, 3,4-dichloro, 2,5-dichloro and 4,5-dichloro-2-methyl.

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