methanolic KOH solution prepared from 0.1 g of KOH and 50 ml of MeOH. The reaction was heated to 60° for 1 hr, during which an additional 36 g (0.50 mole) of butyraldehyde was added since glpc indicated the butyraldehyde was undergoing self-condensation to 2-ethyl-2-hexenal. The mixture stood at room temperature for 2.5 days. Addition of 85% H_3PO_4 until acidic, stripping of the solvent, and vacuum distillation afforded 17 g (35%) of liquid VI, bp 125–128° (0.05 mm). *Anal.* ($C_{12}H_{15}Cl_2N$) N; Cl: calcd, 29.6; found, 28.5.

2-(2,4-Dichlorophenyl)-3-propylglycidamide (73).—A stirred mixture of 6.0 g (0.025 mole) of VI, 5 ml of 30% H_2O_2, 10 ml of Na_2CO_3 solution, and 30 ml of AcMe was heated at 52° for 30 min. Cooling, filtration of the resultant white crystals, and recrystallization from EtOH gave 3.5 g of **73**, mp 161–162°. The original filtrate afforded an additional 2.5 g of **73**, mp 160–161°, from C_8H_{14}–C_6H_6. The total yield was 6.0 g (88%).

Acknowledgments.—The authors wish to express their appreciation to Dr. W. E. Adcock, Mr. R. J. Convers, and Mr. H. G. Durham for their assistance in the preparation of several of the compounds described herein, to Mr. Paul Saliman and associates for the microanalyses, and to Mr. J. E. Hassen, Mr. L. T. Lais, and Mr. S. M. Stearns for their assistance in the biological evaluation of these compounds.

Analgetics. II. Relationship between Structure and Activity of Some β-Amino Ketones[1,2]

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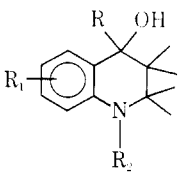
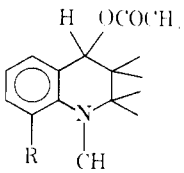
A number of substituted 1,2,3,4-tetrahydro-4-quinolinols and related compounds were prepared and found devoid of analgetic activity. The successful synthesis of a series of β-aminopropiophenones, considered to be open-chain analogs of active 2,3-dihydro-4-quinolones, yielded compounds more potent than their closed-ring analogs.

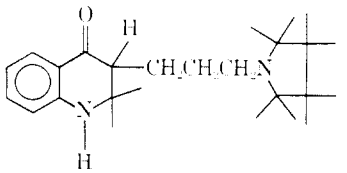
The reported analgetic activity of several 2,3-dihydro-4-quinolones[3] suggested the synthesis and biological examination of a number of analogous compounds. Those studied include a series of 1,2,3,4-tetrahydro-4-quinolinols (I), esters of two of these alcohols (II), a 2,3-dihydro-4-quinolone substituted at C-3 by an ω-N-pyrrolidinopropyl group (III), a series of β-aminopropiophenones (IV), and three 1-alkyloctahydro-4-quinolones (V).



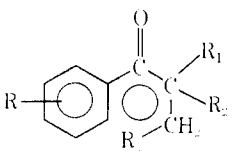
I, R = H, C_6H_5, $C_6H_5CH_2$, *n*-C_4H_9
R_1 = H, OCH_3
R_2 = H, alkyl, alkenyl or acyl



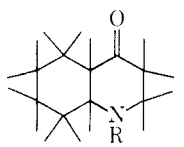
II, R = H or OCH_3



III



IV, R = H, OCH_3, or OH
R_1 and R_2 = H or CH_3
R_3 = alkylamino or dialkylamino



V, R = CH_3, C_2H_5, *n*-C_3H_7

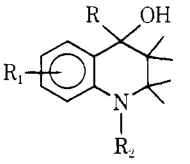
The 1,2,3,4-tetrahydro-4-quinolinols (Table I) were prepared from the corresponding ketone by $NaBH_4$ reduction (method A) or by the addition of a Grignard reagent (method B). While we were unable to esterify the tertiary alcohols, two of the secondary alcohols were converted successfully by CH_2CO to the corresponding acetates. A 2,3-dihydro-4-quinolone having a pyrrolidinopropyl group in the 3 position was prepared by aluminum isopropoxide oxidation of the previously reported[3] 3-[3-(N-pyrrolidinopropyl)]-1,2,3,4-tetrahydro-4-quinolinol.

(1) This investigation was supported in whole by Public Health Service Grant AM 06432-03 from the National Institute of Arthritis and Metabolic Diseases.

(2) Portions of this report were abstracted from the Ph.D. dissertations of M. S. Atwal and M. Megahy, and the M.S. dissertation of C. Pokorny.

(3) M. S. Atwal, L. Bauer, S. N. Dixit, J. E. Gearien, and R. W. Morris, *J. Med. Chem.*, **8**, 566 (1965).

TABLE I
PHYSICAL PROPERTIES OF



No.	R	R_1	R_2	Method	Bp (mm) or mp,[a] °C	Yield, %	Formula[b]	Hydrobromides: Mp,[a] °C	Hydrobromides: Formula[a]
1	H	H	H	A	155–157 (0.5), 78–79[b]	72	$C_9H_{11}NO$	85–86[f]	$C_9H_{12}BrNO$
2	H	H	C_6H_5CO	A	118–119[b]	69	$C_{16}H_{15}NO_2$		
3	H	H	p-$CH_3C_6H_4SO_2$	A	197–198[c]	69	$C_{16}H_{17}NO_3S$		
4	H	7-OCH_3	CH_3	A	145–150 (0.2)	65		83–84[f]	$C_{11}H_{16}NO_2Br$
5	H	8-OCH_3	CH_3	A	67–68[d]	63	$C_{11}H_{15}NO_2$	111–112[f]	$C_{11}H_{16}NO_2Br$
6	H	7-OCH_3	H	A		58		151–152[f]	$C_{10}H_{14}NO_2Br$
7	H	8-OCH_3	H	A		60		98–99[f]	$C_{10}H_{14}NO_2Br$
8	H	7-OCH_3	$CH_2C_6H_5$	A		75		121–122[f]	$C_{17}H_{20}NO_2Br$
9	H	8-OCH_3	$CH_2CH{=}CH_2$	A	65–66[d]	55	$C_{13}H_{17}NO_2$		
10	H	H	$CH_2CH{=}CH_2$	A	100–112 (0.01)	58	$C_{12}H_{15}NO$		
11	H	7-OCH_3	$CH_2CH{=}CH_2$	A	120–124 (0.01)	58	$C_{13}H_{17}NO_2$		
12	H	H	CH_3	A	135–140 (0.05)	71	$C_{10}H_{13}NO$		
13	$C_6H_5CH_2$	H	CH_3	B	167–170 (0.2)	58	$C_{17}H_{19}NO$	206–208[g]	$C_{17}H_{20}BrNO$
14	C_6H_5	H	CH_3	B	165–170 (0.15)	81	$C_{17}H_{17}NO$		
15	C_4H_9	H	CH_3	B	150–155 (0.2)	55	$C_{14}H_{21}NO$		
16	C_6H_5	8-OCH_3	CH_3	B	165–167 (0.2), 83–84[e]	67	$C_{17}H_{19}NO_2$		
17	C_6H_5	H	p-$CH_3C_6H_4SO_2$	B	131–132[e]	76	$C_{22}H_{21}NO_3S$		

[a] All compounds were analyzed for C, H, N. [b] Recrystallized from C_6H_6–ligroin. [c] Recrystallized from EtOH. [d] Recrystallized from Et_2O–ligroin. [e] Recrystallized from ligroin. [f] Recrystallized from MeOH–Et_2O. [g] Recrystallized from $CHCl_3$–Et_2O.

β-Aminopropiophenones were prepared by treating the properly substituted acetophenone with CH_2O and the desired amines (Table II). β-Phenyl-β-aminopropiophenones were synthesized by the addition of the requisite amine to the corresponding chalcone (Table II).

The 1-alkyloctahydro-4-quinolones were prepared by the reaction of 1-acetylcyclohexene, formaldehyde, and the desired amine by a procedure similar to that reported by Grabe and Lutz.[4] Since these amines or their salts in the absence of CH_2O failed to add to the double bond of 1-acetylcyclohexene, it appears that the expected Mannich reaction occurred first, followed by cyclization to give 1-alkyloctahydro-4-quinolones. 1-Methyloctahydro-4-quinolone has been previously characterized by Smissman, *et al.*,[5] who, because of the presence of Bowman bands in its infrared spectrum, has suggested a *trans* structure. Similar bands are found in the infrared spectra of 1-ethyl- and 1-propyloctahydro-4-quinolone.

Biological Activity.—The compounds prepared in this study were evaluated for analgetic activity by the Haffner tail pinch method[6] on female Swiss white mice and were administered by interperitoneal injection.

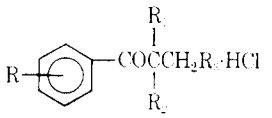
The 1,2,3,4-tetrahydro-4-quinolinols, the esters, and the 3-(N-pyrrolidinopropyl)-2,3-dihydroquinoline, despite their structural resemblance to the previously reported 2,3-dihydro-4-quinolones, failed to show analgetic activity. This lack of activity coupled with the low potency of the 2,3-dihydro-4-quinolones (ED_{50} values over 200 mg/kg) prompted us to examine the open-chain analogs of the biologically active 2,3-dihydro-4-quinolones. It was hoped that such compounds might achieve a better fit on the receptor site than would the previously examined compounds possessing a rigid ring system. In order to test this hypothesis, it was decided to prepare a series of substituted β-aminopropiophenones (Table II). These compounds contain the ketone function, the benzene ring, and the amino group which were also present in the active 1-methyl-2,3-dihydro-4-quinolones, but because of free rotation, the amino group can assume any number of spatial relationships with respect to the carbonyl group and the benzene ring. The importance of these groups to analgetic activity was at least partially established by evaluating the analgetic activity of a number of compounds analogous to 1-methyl-8-methoxy-2,3-dihydro-4-quinolone or its biologically active analogs but lacking in each case one of the groups which were assumed to be necessary for analgetic activity. For example, 1-methyl-8-methoxy-1,2,3,4-tetrahydroquinoline,[7] a compound lacking the carbonyl group, was devoid of activity. The importance of the amino group and the size of the substituent attached to it was realized earlier when it was found that alterations of the alkyl group on the nitrogen drastically affected the activity of the substituted 2,3-dihydro-4-quinolones.[3] Furthermore, when the amino group was deleted from otherwise similarly constituted ring systems, such as in 5- and 6-methoxy-1-tetralones, no analgetic properties could be detected by our testing procedure. The lack of analgetic activity in 1-methyl-, 1-ethyl-, and 1-propyloctahydro-4-quinolones, as found by us, indicates the importance of the aromatic ring.

The presence of analgetic activity (Table II) in β-

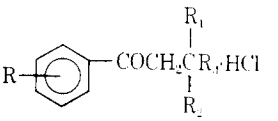
(4) C. A. Grabe and H. J. Lutz, *Helv. Chim. Acta*, **48**, 791 (1963).
(5) E. E. Smissman and M. Steinman, *J. Med. Chem.*, **9**, 455 (1966).
(6) C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9**, 280 (1954).
(7) O. Fisher and C. A. Kohn, *Ber.*, **19**, 1040 (1886).

TABLE II

PHYSICAL PROPERTIES AND ANALGETIC PROPERTIES OF



No.	R	R_1	R_2	R_3	Crystn solvent[a]	Mp, °C	% yield	Formula[b]	Analgesia ED_{50},[c] mg/kg	LD_{50},[c] mg/kg
18	4-OCH$_3$	H	H	$N(CH_3)_2$	A	178–180[d]	48		150	275
19	4-OCH$_3$	H	H	$N(C_2H_5)_2$	A	119–120[e]	60		*i*	180
20	4-OCH$_3$	H	H	$N(CH_2)_5$	B	210–211[e]	23		110	137
21	4-OCH$_3$	H	H	$NHCH_3$	C	155–157[f]	46		315	*j*
22	4-OCH$_3$	H	H	NHC_2H_5	B	175–176	45	$C_{12}H_{15}ClNO_2$	380	*j*
23	4-OCH$_3$	H	H	$NHCH_2C_6H_5$	C	170–172	59	$C_{17}H_{20}ClNO_2$	65	175
24	4-OCH$_3$	H	H	$NH(CH_2)_2C_6H_5$	D	164–166	61	$C_{18}H_{22}ClNO_2$	*i*	90
25	2-OH	H	H	$N(CH_3)_2$	B	156–157	36	$C_{11}H_{16}ClNO_2$	360	640
26	2-OH	H	H	$NHCH_3$	C	153–155	37	$C_{10}H_{14}ClNO_2$	200	400
27	2-OH	H	H	NHC_2H_5	A	186–188	52	$C_{11}H_{16}ClNO_2$	100	370
28	2-OH	H	H	$NHCH_2C_6H_5$	E	180–182	58	$C_{16}H_{18}ClNO_2$	*i*	160
29	H	CH_3	CH_3	$N(CH_3)_2$	F	137–140[g]	37		16	85
30	H	CH_3	CH_3	$N(C_2H_5)_2$	A	131–133	36	$C_{15}H_{24}ClNO$	93	187
31	H	CH_3	CH_3	$NHCH_3$	E	133–136	50	$C_{12}H_{18}ClNO$	115	130
32	H	CH_3	CH_3	NHC_2H_5	A	116–118	54	$C_{13}H_{20}ClNO$	*i*	155



33	H	H	C_6H_5	$N(CH_2)_5$	A	127–129	61	$C_{20}H_{24}ClNO$	*i*	*j*
34	H	H	*p*-$CH_3OC_6H_4$	$N(CH_2)_5$	G	169–172	51	$C_{21}H_{26}ClNO_2$	238	345
35	4-OCH$_3$	H	C_6H_5	$N(CH_2)_5$	F	159–161	37	$C_{21}H_{26}ClNO_2$	*i*	170
36	4-OCH$_3$	H	C_6H_5	$NHCH_3$	G	139–141	65	$C_{17}H_{20}ClNO_2$	*i*	140
37	H	H	*p*-$CH_3OC_6H_4$	$NHCH_2C_6H_5$	C	145–146	35	$C_{24}H_{24}ClNO_2$	*i*	870
38	4-OCH$_3$	H	C_6H_5	$NHCH_2C_6H_5$	C	168–171	39	$C_{25}H_{24}ClNO_2$	*i*	770

[a] A = absolute EtOH–dry Et_2O, B = absolute EtOH, C = MeOH–Me_2CO, D = MeOH, E = MeOH–C_6H_6, F = Me_2CO–dry Et_2O, G = Me_2CO–$CHCl_3$. [b] All compounds were analyzed for C, H, N, Cl, and each element analyzed within 0.4% of the theoretical value. [c] ED_{50} and LD_{50} values were determined by intraperitoneal injection of the compound to female white mice. They were determined by the method of J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949). [d] C. Mannich and D. Lammering, *Ber.*, **55**, 3510 (1922), reported mp 181°. [e] A. N. Kost and V. V. Ershov, *Vestn. Mask. Un-ta., Ser. Fiz. Mat. i Estestven. Nauk*, **10**, 115 (1955); *Chem. Abstr.*, **50**, 11320 (1956), found mp 119°. [f] A melting point of 211–213° had previously been reported by T. Okudo, *J. Pharm. Soc. Japan*, **76**, 4 (1956); *Chem. Abstr.*, **50**, 13 (1956). [g] I. Satoda, *Yakugaku Zasshi*, **80**, 1 (1960); *Chem. Abstr.*, **54**, 12141 (1960), reported mp 156–157°. [h] I. N. Nazarov, E. Cherkasova, and C. Chan, *Zh. Obshch. Khim.*, **28**, 452 (1958); *Chem. Abstr.*, **52**, 15515 (1958), reported mp 138–140°. [i] Inactive. [j] Not toxic at doses up to 500 mg/kg.

aminoacetophenones appears to give credence to the hypothesis that the rigid ring systems of the 2,3-dihydroquinolones did not permit an optimal fit on a receptor site. A number of these open-chain β-amino ketones (**18**, **20**, **23**, and **27**) possessed analgetic activity considerably greater than the previously examined 2,3-dihydro-4-quinolones.

While some of the β-aminopropiophenones exhibited greater analgetic activity than did the previously prepared 1-methyl-2,3-dihydro-4-quinolones, their action appears to be of short duration (less than 0.5 hr in mice). The structure of these compounds suggested that this rather fleeting action might be due to rapid detoxification possibly by (1) oxidation of the side chain or (2) elimination of the substituted amino group. In the hope of hindering such detoxification and providing compounds of longer duration of action, several α,α-disubstituted β-aminopropiophenones were prepared and examined for analgesic activity. These had a duration of action of over 2 hr, and α,α-dimethyl-β-(dimethylamino)propiophenone (**29**) was the most potent compound prepared in this study. It had an ED_{50} of 16 mg/kg which is approximately twice that of morphine sulfate when determined under similar conditions.

An attempt to improve the activity of the compounds by substituting a phenyl group for a hydrogen atom on the β-carbon of a number of β-aminopropiophenones resulted in inactive compounds with the exception of β-(*p*-methoxyphenyl)-β-(1-piperidino)propiophenone (**34**) which had an ED_{50} of 238 mg/kg.

Experimental Section[a]

1,2,3,4-Tetrahydro-4-quinolinols. Method A. Reduction of 2,3-Dihydro-4-quinolones.—$NaBH_4$ reduction of the appropriately substituted 2,3-dihydro-4-quinolones[3] yielded the corresponding alcohols. This is illustrated by the procedure employed for the preparation of 1,2,3,5-tetrahydro-4-quinolinol.

To a stirred solution of 2,3-dihydro-4-quinolone (14.7 g, 0.1 mole) in anhydrous MeOH (100 ml) was gradually added $NaBH_4$ (6.8 g, 0.2 mole). The reaction mixture was kept at 0° for 18 hr. H_2O (120 ml) was added and the mixture was extracted several

[a] Melting points are not corrected and were obtained on a Thomas–Hoover melting point apparatus. Analyses are indicated only by symbols of the elements, the analytical results obtained from these determinations are within 0.40% of the theoretical value.

times with Et_2O. The combined Et_2O extracts were washed with H_2O and dried ($MgSO_4$). After evaporation of the solvent, the residue was distilled to yield 10.6 g (72%) of a white solid. After recrystallization from C_6H_6–ligroin (bp 67–75°) it melted at 78–79°.

Method B. Grignard Reaction.—1,2,3,4-Tetrahydro-4-quinolinols with an alkyl or aryl group in the 4 position were prepared by the reaction of the appropriately substituted 2,3-dihydro-4-quinolone[3] with a Grignard reagent. The procedure employed for the synthesis of 1-methyl-4-benzyl-1,2,3,4-tetrahydro-4-quinolinol will serve as an example.

In a flask in which the air has been replaced with N_2 was placed anhydrous Et_2O (20 ml) and Mg turnings (3.6 g, 0.15 g-atom). This suspension was stirred and a solution of benzyl chloride (19.0 g, 0.15 mole) in Et_2O (10 ml) was added dropwise. When the reaction ceased, the mixture was added slowly under N_2 to a solution of 1-methyl-2,3-dihydro-4-quinolone (8.0 g, 0.05 mole) in anhydrous Et_2O (40 ml). After the reaction ceased, the solution was heated under reflux for 4 hr and was then cooled to 0° and decomposed by the addition of H_2O. The organic layer was separated, washed with H_2O, and dried ($MgSO_4$). The Et_2O was removed and the residue distilled to yield 7.3 g (58%) of 1-methyl-4-benzyl-1,2,3,4-tetrahydro-4-quinolinol (see Table I).

1-Methyl-4-acetoxy-1,2,3,4-tetrahydroquinoline Hydrobromide.—A solution of 1-methyl-1,2,3,4-tetrahydro-4-quinolinol (1.5 g, 0.01 mole) in anhydrous Et_2O (150 ml) was cooled in an ice bath and a stream of CH_2CO was passed through the solution for 6 hr. The solvent was removed *in vacuo* at 0° and the residue was chromatographed from alumina (Alcoa F-20). After elution with a 1:3 mixture of C_6H_6–2-PrOH, 0.9 g (42%) of an oil was obtained. *Anal.* ($C_{12}H_{15}NO_2$).

The hydrobromide was prepared in the usual manner. After recrystallization from $CHCl_3$–Et_2O, it melted at 119–120°. *Anal.* ($C_{12}H_{16}BrNO_2$) C, H, N.

1-Methyl-8-methoxy-4-acetoxy-1,2,3,4-tetrahydroquinoline Hydrobromide.—A solution of 1-methyl-8-methoxy-1,2,3,4-tetrahydro-4-quinolinol (2.0 g, 0.008 mole) in Et_2O (100 ml) was treated with CH_2CO at 0° as described in the last preparation. After removal of most of the Et_2O, the residue was treated with anhydrous HBr to yield 2.0 g (63%) of the desired salt. After two recrystallizations from MeOH–Et_2O, the white solid melted at 106–107°. *Anal.* ($C_{13}H_{18}NO_3Br$) C, H, N.

3-[3-(N-Pyrrolidinopropyl)]-2,3-dihydro-4-quinolone.—To a solution of 3-[3-(N-pyrrolidinopropyl)]-1,2,3,4-tetrahydro-4-quinolinol[3] (4.5 g, 0.017 mole) in Me_2CO (200 ml) and dry C_6H_6 (300 ml) was added aluminum isopropoxide (9.0 g, 0.044 mole). The resulting mixture was heated under reflux for 40 hr. Solvents were distilled off and the residue was extracted several times with Et_2O. The Et_2O extracts were washed with 5% NaOH, then with H_2O, and dried (Na_2SO_4). After removal of the Et_2O, the residue was recrystallized from Et_2O–ligroin to give colorless crystals (2.0 g, 45%), mp 102–103°. *Anal.* ($C_{16}H_{22}N_2O$) C, H, N.

1-Methyloctahydro-4-quinolone.—A mixture of 1-acetylcyclohexene (12.4 g, 0.1 mole), $MeNH_2 \cdot HCl$ (6.7 g, 0.1 mole), and paraformaldehyde (5.0 g) in 50 ml of absolute EtOH was boiled under reflux for 16 hr. Solvents were removed and the mixture was treated with 10% HCl (100 ml). The resulting solution was extracted with Et_2O and the Et_2O was discarded. The aqueous layer was made alkaline with NaOH and was extracted with Et_2O. The Et_2O extract was dried (Na_2SO_4) and distilled. A fraction boiling at 85–92° (0.5 mm) was collected. It weighed 9.2 g (55%) and possessed an ir spectrum identical with that reported previously.[5]

1-Ethyloctahydro-4-quinolone.—A similar reaction of 1-acetylcyclohexene (12.4 g, 0.1 mole), $EtNH_2 \cdot HCl$ (8.2 g, 0.1 mole), and paraformaldehyde (5.0 g) in 50 ml of absolute ethanol as described above for 1-methyloctahydro-4-quinolone yielded upon distillation an oil (11.2 g, 62%), bp 93–99° (0.5 mm). A picrate of the oil was prepared in the usual manner, mp 182–184°. *Anal.* ($C_{17}H_{22}N_4O_8$) C, H, N.

1-Propyloctahydro-4-quinolone.—When 1-acetylcyclohexene (412.4 g, 0.1 mole), $PrNH_2$ (6.0 g, 0.1 mole), paraformaldehyde (5.0 g), and 10 ml of HCl were refluxed with 50 ml of absolute EtOH following the procedure employed for the synthesis of 1-methyloctahydro-4-quinolone, 10.5 g (54%) of the product was obtained. It boiled at 102–110° (0.5 mm).

A picrate was prepared by the usual procedure. It melted at 157–159° after recrystallization from C_6H_6. *Anal.* ($C_{18}H_{24}N_4O_8$) C, H, N.

Synthesis of β-Aminopropiophenones.—A mixture of the appropriate acetophenone (0.1 mole) and the amine hydrochloride (0.15 mole) was heated in EtOH (15 ml) at the reflux. Paraformaldehyde (3.6 g) was added and the resulting mixture was heated for 7 hr. Another portion of paraformaldehyde (1.5 g) was added and the heating was continued for an additional 2 hr. At this time 1 ml of HCl was added and the heating was continued for an additional 2 hr, after which the solvent was evaporated and the residue was dissolved in 20 ml of H_2O. This aqueous solution was washed twice with an equal volume of Et_2O, cooled, made alkaline with 50% NaOH solution, and extracted with Et_2O. The Et_2O solution was washed with water and dried (Na_2SO_4).

On passing HCl through the filtered Et_2O solution, the hydrochloride salt was precipitated and was purified by recrystallization.

α,α-Dimethyl-β-aminopropiophenones were prepared from isobutyrophenones, $Me_2NH \cdot HCl$, and paraformaldehyde by a procedure identical with that employed for the preparation of the β-aminopropiophenones.

Preparation of β-Aryl-β-aminopropiophenones.—The appropriate benzalacetophenone (0.06 mole) and the amine (0.08 mole) were dissolved in 50 ml of anhydrous Et_2O and heated under reflux for 10 hr. Toluene (20 ml) was added and the solvents were evaporated *in vacuo*. Additional portions of toluene were added and removed by distillation *in vacuo* until the distillate gave a negative test for the amine. The residue was then dissolved in dry Et_2O and the hydrochloride precipitated in the usual manner. The salt was purified by recrystallization.