For chromatographic purposes, two 10-ml portions of a strong anion-exchange resin (amberlite IRA 400) were each washed with 100 ml of 1 N carbonate-free NaOH to be certain the resin was in the OH form of the cycle and then with 200 ml of water until the washes were neutral. Two-milliliter volumes (containing approximately 15 mg of protein with attached boron hydride anions) were passed through the resin columns, and volumes of 25–100 ml were collected. Aliquots were analyzed for boron content.

Acute toxicity studies in CD1 male (Swiss Albino) mice were carried out by a physiological saline.

For rabbit toxicity studies, male and female New Zealand white rabbits weighing between 2.1 and 3.1 kg were used. The cesium salt of the $B_{12}H_{11}SH^{2-}$ anion was converted to its sodium salt by ion-exchange resins and an isotonic solution of this compound at pH 7.2 was sterilized by passage through a Millipore filter (pore size: 0.45 μ) prior to its injection into the ear vein of the rabbit. A dose of 40 mg of boron/kg was administered daily for 5 successive days and then the animals were observed for 30 days following the last injection.

Acknowledgments.—The authors wish to thank Dr. William H. Sweet, Professor of Surgery at the Harvard Medical School and Chief of the Neurosurgical Service of the Massachusetts General Hospital for his great interest and support of this work. The invaluable technical assistance of Mrs. Janette R. Messer and her collaborators, Misses Beverly Whitman, Mary Hagney, and Barbara Greene, is gratefully acknowledged.

Maleamic Acids That Affect Plasma Cholesterol and Penicillin Excretion

EVERETT M. SCHULTZ,[1] WILLIAM A. BOLHOFER, ALBERT AUGENBLICK, JOHN B. BICKING, CHARLES N. HABECKER, J. KENNETH HORNER, SARA F. KWONG, AND ADOLPH M. PIETRUSZKIEWICZ

Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., West Point, Pennsylvania

Received January 16, 1967

A number of maleamic acids have been prepared by the reaction of maleic anhydride with an appropriate amine. In general, the amines are of the di- and triphenyl-substituted alkyl type for which synthetic procedures are given. Some of these have two asymmetric centers and in most instances both of the racemates were obtained in pure form. Compounds were prepared to show the biological effect of (a) the degree of substitution on the amide nitrogen atom, (b) systematic variation of substituents on the carbon atom α to it, and (c) variation in the positions of the aryl groups on the alkyl chain of the amine. For comparison purposes, the fumaramic acid analog of one of the most active maleamic acids and the succinamic acid analog of another were prepared. The hypocholesterolemic activity in rats and/or the inhibitory effect on penicillin excretion in dogs is reported. Structure–activity relationships are developed and biological effects of the major structural variations are emphasized. One of the maleamic acids, N-[2,3-bis(*p*-chlorophenyl)-1-methylpropyl]maleamic acid (benzmalecene) has been the subject of clinical investigation.

The effect of a maleamic acid, benzmalecene,[2] on penicillin excretion, uric acid transport, and plasma cholesterol in the dog, plasma cholesterol in the rat, and on the *in vitro* synthesis of cholesterol from mevalonic acid in rat liver homogenates has been reported from these laboratories.[3,4]

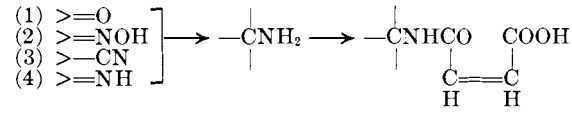
The action of benzmalecene on microbiological systems has been reported by Aaronson, *et al.*,[5] and by Holz, *et al.*[6] Inhibition of the active transport of bile acids across the intestinal mucosa by a number of maleamic acids has been studied by Lack and Weiner.[7]

Clinical evaluation in man has shown that benzmalecene has a hypocholesterolemic action,[8] inhibits the excretion of penicillin,[9] and has a uricosuric effect,[9,10] which, however, is not reflected in a decrease of blood uric acid levels.[9]

Benzmalecene (**1**, Table II) is a representative member of a series of related maleamic acids. The synthesis of other members of the series along with data for their inhibitory action on penicillin excretion in dogs and/or the hypocholesterolemic activity in rats comprise the subject matter of the present report.

All of the maleamic acids were prepared by the reaction of an amine with maleic anhydride. The appropriate amines were obtained from various precursors by procedures such as (1) the Leuckart reaction on an appropriate ketone, (2) catalytic hydrogenation of a corresponding ketoxime, (3) reduction of a nitrile, and (4) hydrogenation of a corresponding ketimine. These transformations are depicted diagramatically in Scheme I. The intermediate ketones, ketoximes

SCHEME I



(Table I), nitriles, and ketimines were prepared by standard procedures, the details of which are set forth in the Experimental Section. Known amines were pre-

(1) To whom inquiries should be addressed.

(2) Benzmalecene is the generic name for N-[2,3-bis(*p*-chlorophenyl)-1-methylpropyl]maleamic acid (α isomer): E. M. Schultz, J. B. Bicking, and V. D. Wiebelhaus, British Patent 901,438 (July 18, 1962).

(3) J. E. Baer, H. F. Russo, A. V. Brooks, and K. H. Beyer, *Pharmacologist*, **1**, No. 2, 53 (1959).

(4) J. W. Huff and J. L. Gilfillan, *Proc. Soc. Exptl. Biol. Med.*, **103**, 41 (1960).

(5) S. Aaronson, B. Bensky, and M. Shifrine, *ibid.*, **109**, 130 (1962); S. Aaronson, *J. Gen. Microbiol.*, **37**, 225 (1964); **39**, 367 (1965); *Nature*, **202**, 1355 (1964).

(6) G. G. Holz, Jr., L. Rasmussen, and E. Zeuthen, *Compt. Rend. Trav. Lab. Carlsberg*, **33**, 290 (1963).

(7) L. Lack and I. M. Weiner, *J. Pharmacol. Exptl. Therap.*, **139**, 248 (1963); *Federation Proc.*, **21**, 258 (1962).

(8) S. S. Bergen, Jr., T. B. Van Itallie, and W. H. Sebrell, *Proc. Soc. Exptl. Biol. Med.*, **103**, 39 (1960); S. S. Bergen, Jr., and T. B. Van Itallie, *Ann. Internal Med.*, **58**, 355 (1963); E. E. Cooper, *Circulation*, **20**, 681 (1959); R. H. Furman, R. P. Howard, L. N. Norcia, and C. W. Robinson, Jr., *Proc. Soc. Exptl. Biol. Med.*, **103**, 302 (1960); *J. Lab. Clin. Med.*, **54**, 817 (1959); I. H. Page and R. E. Schneckloth, *Circulation*, **20**, 1075 (1959); B. A. Sacks, E. Danielson, and R. J. Sperber, *Metab. Clin. Exptl.*, **9**, 783 (1960); *Circulation*, **20**, 762 (1959).

(9) P. E. Siegler, J. B. Rosenfeld, D. Naide, J. DiMarco, and J. H. Nodine, *Current Therap. Res.*, **2**, 448 (1960); *Clin. Exptl. Res.*, **8**, 290 (1960).

(10) J. H. Talbot, *J. Bone Joint Surg.*, **40A**, 994 (1958).

TABLE I

Ketone	Oxime Mp, °C	Oxime Yield, %	Cryst'n solvent
1,2-Diphenyl-3-pentanone[a]	101.5–103	69	85% alcohol
1,3,4-Triphenyl-2-butanone[b]	75–76.5	65	Hexane
3-Benzyl-3-phenyl-2-pentanone	172.5–175	99	Not recryst
1,2,3-Triphenyl-1-propanone[c]	115–134	64	1-Propanol
3-Benzyl-3,4-diphenyl-2-butanone[d]	165.5–168	81	Acetonitrile
3,4,4-Triphenyl-2-butanone	148.5–151	59	2-Propanol
3,3,4-Triphenyl-2-butanone[e]	118–122[f]	65	Cyclohexane
3,4-Bis(*p*-chlorophenyl)-2-butanone	94–96	84	Hexane

[a] E. M. Schultz and J. B. Bicking, *J. Am. Chem. Soc.*, **75**, 1128 (1953). [b] Prepared by alkylating dibenzyl ketone with benzyl chloride in the presence of NaOH in ethyl alcohol by the method of ref 18; yield 72.3%, mp 73–75°; C. R. Hauser and T. M. Harris (*ibid.*, **81**, 1154 (1959)) report mp 73–74.5°. [c] E. J. Cragoe, Jr., A. M. Pietruszkiewicz, and C. M. Robb, *J. Org. Chem.*, **23**, 971 (1958). [d] S. MacKenzie, S. F. Marsocci, and P. R. Santurri, *ibid.*, **28**, 717 (1963). [e] Reference 18. [f] Oxime was isolated as the monohydrate; anhydrous form, mp 142–145°.

pared by methods considered most convenient and productive but not necessarily by procedures documented in the chemical literature. However, reference is always made thereto.

Many of the amines prepared for the present investigation possess two asymmetric carbon atoms and hence may exist in two racemic modifications. None of the preparative procedures was stereospecific and each amine was obtained as a mixture of both modifications. The majority of these were separated and the two racemates were arbitrarily designated for convenience as the α and β isomer. The first to be isolated was always designated as the α isomer and it (and its salts) is usually the higher melting and less soluble of the two. The procedure required for the physical separation of each pair of isomers proved to be unique for each amine and the specific details have been included in the Experimental Section.

As expected, it was found that the proportion of the α:β isomer varied according to the method of preparation of the amine. When 2,3-bis(*p*-chlorophenyl)-1-methylpropylamine was prepared by a Leuckart reaction on 3,4-bis(*p*-chlorophenyl)-2-butanone, the ratio of α:β isomer was 1:3 and this ratio was essentially reversed when the same amine was prepared by catalytic reduction of the oxime of the aforementioned ketone.

Admixture of solutions of an amine and maleic anhydride, usually in ether or benzene, yielded the crystalline maleamic acid in an essentially pure condition. The maleamic acids prepared in this investigation are listed in Table II. Those synthesized from amines having α and β isomeric forms were assigned the same designation as their corresponding amines. The maleamic acids are chemically stable compounds that can be heated for several hours with 1 *N* KOH without significant hydrolysis of the amide function.

The dextrorotatory enantiomorph of the α isomer of N-[3-(*p*-chlorophenyl)-1-methyl-2-phenylpropyl]-maleamic acid (**38**) was prepared by fractional crystallization of the quinine salt. The levorotatory enantiomorph of the α isomer was not isolated.[11]

For biological comparison, the fumaramic acid counterpart (**40**) of benzmalecene (**1**) and the succinamic acid counterpart (**41**) of N-(2,3-diphenyl-1-methylpropyl)maleamic acid α isomer (**7**) were prepared. The fumaramic acid was prepared by treating ethylfumaryl chloride with the α isomer of 2,3-bis(*p*-chlorophenyl)-1-methylpropylamine with subsequent saponification of the ester function. The succinamic acid was prepared in essentially the same manner as the maleamic acid by replacing maleic anhydride with succinic anhydride in the reaction with the amine.

One example of a maleamic acid having two substituents on the amide nitrogen atom, N-(2,3-diphenyl-1-methylpropyl)-N-methylmaleamic acid (**39**), was made. The intermediate amine was prepared by a Leuckart-type reaction of 3,4-diphenyl-2-butanone with N-methylformamide. Only one of the two possible isomers of the amine was isolated and the relationship of the stereochemistry of the 2,3-diphenyl-1-methylpropyl group in this amine to the stereochemistry of the corresponding group in the α and β isomers of 2,3-diphenyl-1-methylpropylamine was not determined.

Biological Results

Inhibition of Penicillin Excretion.[12]—The assay for penicillin excretion inhibition in dogs was carried out by published methods.[13] The results indicate that in the group of maleamic acids investigated, an N-(2,3-diphenyl-1-methylpropyl) moiety is essential for good activity and it is evident that the α isomers (the higher melting isomers) are more active than the corresponding β isomers. For these α isomers, chlorine substituents in both phenyl groups are essential for good oral activity but the intravenous activity is uninfluenced by such substituents. The effect of disubstitution of the amide nitrogen atom was not extensively investigated in the series, but one example (**39**) proved to be inactive. The dextrorotatory form (**38**) of one of the *dl*-α isomers (**5**) showed an activity that was not strikingly different from the *dl* mixture.

Hypocholesterolemic Effects.[14]—The hypocholesterolemic activity of the maleamic acids in rats is tabulated in Table II. Benzmalecene (**1**) is one of the most active compounds of the group, although others have an activity of the same order of magnitude (**2**, **7**, **16**, **17**, **19**, **20**). Benzmalecene and its β isomer (**2**) have essentially the same degree of hypocholesterolemic activity. Other pairs of α and β isomers (**7** and **8**, **10** and **11**, **12** and **13**, **14** and **15**) also appear to have the same or similar activity. Replacement of the maleic acid group of benzmalecene by fumaric acid yields the *trans* isomer (**40**) which has a considerably decreased activity. Succinamic acids appear to be inactive as shown by a comparison of **41** with its corresponding maleamic acid (**7**). The activity of the maleamic acids is particularly sensitive to the degree of substitution on the amide nitrogen and the type of substituent on the carbon atom attached thereto. The lack of activity of **39** in which the amide nitrogen is disubstituted compared to its highly active monosubstituted analog **7** (or **8**) would indicate that only one substituent is allowable for hypocholesterolemic activity

(11) An investigation of the stereochemistry of the 2,3-diphenyl-1-methylpropylamine system has been carried out by S. Pines, *et al.*, *J. Med. Chem.*, **10**, 725 (1967).

(12) These data were provided by Dr. J. E. Baer and staff, Merck Sharp and Dohme Research Laboratories, West Point, Pa.

(13) K. H. Beyer, A. K. Miller, H. F. Russo, E. A. Patch, and W. F. Verwey, *Am. J. Physiol.*, **149**, 355 (1947).

(14) We are indebted to Dr. J. Huff of the Merck Sharp and Dohme Research Laboratories, Rahway, N. J., for making the hypocholesterolemic data available to us.

to be obtained. Comparison of **7**, **9**, **10**, **12**, and **14** very strikingly shows the effect and importance of the lower alkyl substituent on the carbon atom α to the amide nitrogen. A hydrogen atom or an ethyl group on this carbon atom results in a considerable decrease in the potency of the maleamic acid. For maximum activity the methyl group (*e.g.*, **7**) appears to be an essential and almost exclusive requirement. Examination of the data in Table II will reveal several other groups of compounds in which a systematic variation in structure of the amine moiety leads to changes in the degree of activity which show significant trends useful for additional structure–activity correlation.

Experimental Section[15]

1-(*p*-Chlorophenyl)-2-propanone was prepared by the procedure of Hoover and Haas.[16] A mixture of *p*-chlorobenzaldehyde (107 g, 1.01 moles), nitroethane (65 g, 0.86 mole), *n*-butylamine (20 ml), and toluene (200 ml) was refluxed, under a continuous water separator, for 7 hr. The toluene was distilled and methanol (100 ml) was added to the hot residue. The mixture then was cooled at −30° for 16 hr. The yellow precipitate, 1-(*p*-chlorophenyl)-2-nitro-1-propene (108 g, 72%) was collected by filtration and dried by suction. A sample crystallized from methanol (4 ml/g) melted at 84–85°.

A mixture of the crude nitropropene (108 g, 0.55 mole), iron powder (20 mesh) (210 g), $FeCl_3$ (1 g), and water (630 ml) was refluxed with stirring for 12 hr during which time concentrated HCl (116 ml) was added in small portions. The mixture then was submitted to steam distillation. The product was extracted from the distillate with benzene. The benzene extract was dried (Na_2SO_4), the solvent was evaporated, and the residue was distilled. The 1-(*p*-chlorophenyl)-2-propanone, bp 79–81° (0.3 mm), $n^{22}D$ 1.5352–1.5358, amounted to 56 g (61%).[17]

1-(*p*-Butoxyphenyl)-2-propanone was prepared by the procedure described for the *p*-chlorophenyl analog. *p*-Butoxybenzaldehyde reacted with nitroethane to provide **1-(*p*-butoxyphenyl)-2-nitro-1-propene**, mp 53–55°.

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.35; H, 7.28; N, 5.95. Found: C, 66.43; H, 7.36; N, 5.91.

Reduction with iron and acid produced the desired ketone, bp 120–123° (2 mm). The **2,4-dinitrophenylhydrazone** melted at 119–121°.

Anal. Calcd for $C_{19}H_{22}N_4O_5$: C, 59.06; H, 5.75; N, 14.50. Found: C, 59.19; H, 5.77; N, 14.48.

3,4-Bis(*p*-chlorophenyl)-2-butanone.—To a stirred mixture of granulated NaOH (36.8 g, 0.92 mole) and 1-(*p*-chlorophenyl)-2-propanone (141.6 g, 0.84 mole) there was added slowly *p*-chlorobenzyl chloride (161 g, 1.0 mole) while the internal temperature of the reaction mixture was maintained at 25–30° by intermittent cooling with a water bath. When all had been added and the temperature no longer rose spontaneously, the mixture was heated at 80–90° (steam bath) with stirring for 5 hr. Water (150 ml) was added to the cooled mixture, the yellow oil was extracted with ether, and the ether extract was dried (Na_2SO_4) and evaporated. The residue was distilled to obtain 3,4-bis-(*p*-chlorophenyl)-2-butanone in 64% yield, bp 170° (0.3 mm). The **2,4-nitrophenylhydrazone** melted at 154–155°.

Anal. Calcd for $C_{22}H_{18}Cl_2N_4O_4$: C, 55.82; H, 3.84; Cl, 14.98. Found: C, 56.16; H, 3.87; Cl, 15.01.

3-(*p*-Chlorophenyl)-4-phenyl-2-butanone was prepared in 64% yield by alkylating 1-(*p*-chlorophenyl)-2-propanone (45 g, 0.27 mole) with benzyl chloride (44 g, 0.3 mole) by the procedure described for 3,4-bis(*p*-chlorophenyl)-2-butanone. The product, after crystallization from 2-propanol, melted at 80–81°.

Anal. Calcd for $C_{16}H_{15}ClO$: C, 74.28; H, 5.75. Found: C, 74.02; H, 5.95.

4-(*p*-Chlorophenyl)-3-phenyl-2-butanone.—Phenylacetone was alkylated with *p*-chlorobenzyl chloride by the procedure described above. The ketone boiled at 148–151° (0.3 mm) and melted at 78–79° after crystallization from ethanol. The yield was 44%.

Anal. Calcd for $C_{16}H_{15}ClO$: C, 74.28; H, 5.75. Found: C, 74.42; H, 5.83.

3,4,4-Triphenyl-2-butanone.—Phenylacetone (206 g, 1.53 moles) was added to a solution of 70 g (1.51 moles) of commercial potassium *t*-butoxide in 700 ml of dry *t*-butyl alcohol. The temperature rose to 45° and benzhydryl chloride (304 g, 1.50 moles) was added over a 25-min period. Occasional cooling was necessary to maintain the temperature at 50–60°. After an additional 30 min, the reaction was heated under reflux for 1.5 hr and the solvent was removed under reduced pressure. Water was added to the residue and the product was extracted with ether. The extract was concentrated and the residue distilled. Material boiling in the range of 171–194° (0.5 mm) was collected (259 g) and crystallized from about 1 l. of isopropyl alcohol. The crystalline product (199 g, 44% yield) melted at 130–134°. A pure sample was made by recrystallization from *n*-propyl alcohol, mp 131–132.5°.

Anal. Calcd for $C_{22}H_{20}O$: C, 87.96; H, 6.71. Found: C, 87.92; H, 6.61.

3-Benzyl-3-phenyl-2-pentanone.—3-Phenyl-2-pentanone[18] in *t*-butyl alcohol solution was alkylated with benzyl chloride using potassium *t*-butoxide under the conditions described for the preparation of 3,4,4-triphenyl-2-butanone. The product was obtained as an oil which was distilled. The fraction boiling at 143–160° (1.5 mm) was collected and crystallized from two volumes of hexane. Crystalline product, mp 84.5–87.5°, was obtained in 33.7% yield. Additional recrystallization raised the melting point to 87.5–89°.

Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.88; H, 8.10.

1,1-Diphenyl-3-hexanone.—Phenylmagnesium bromide was allowed to react with 1-phenyl-1-hexen-3-one by the method described by Kohler[19] to obtain the desired ketone, bp 135–140° (0.2 mm). The once-distilled product was used directly in the Leuckart reaction.

1-Cyclohexyl-3,3-diphenyl-1-propanone.—A Grignard reagent was prepared from cyclohexyl bromide (58.8 g, 0.24 mole) and Mg (8.64 g, 0.36 g-atom) in ether (160 ml). Then a solution of β,β-diphenylpropionitrile (50 g, 0.24 mole) in benzene (200 ml) was added over 0.5 hr to the stirred, boiling ether Grignard solution. The ether was distilled and the residual benzene solution was refluxed for 24 hr. The mixture was cooled and added to a mixture of 12 *N* HCl (200 ml) and ice (500 g). Three layers formed. The upper benzene layer was removed. The lower aqueous layers were heated at 80–90° for 16 hr and then extracted with ether. This ether extract and the original benzene extract were combined, dried (Na_2SO_4), and evaporated. The residue was extracted with two 150-ml portions of boiling hexane. The extracts were filtered hot and the filtrate was heated with decolorizing carbon, filtered, and evaporated. The residue was crystallized from ligroin. The product (25 g) melted at 63–64°.

Anal. Calcd for $C_{21}H_{24}O$: C, 86.25; H, 8.27. Found: C, 86.21; H, 8.18.

3-(*p*-Butoxyphenyl)-4-methyl-2-pentanone was prepared from 1-(*p*-butoxyphenyl)-2-propanone and isopropyl iodide in *t*-butyl alcohol in the presence of potassium *t*-butoxide by a procedure previously reported.[18] The ketone boiled at 119–124° (1 mm). The **2,4-dinitrophenylhydrazone** melted at 67–69°.

Anal. Calcd for $C_{22}H_{28}N_4O_5$: C, 61.66; H, 6.59. Found: C, 61.49; H, 6.64.

Preparation of Oximes.—A generally applicable procedure was used for the preparation of oximes. The ketone was dissolved in 5 vol. of *n*-propyl alcohol and 5 vol. of pyridine. An equal weight of hydroxylamine hydrochloride was added and the mixture was heated under reflux for 18 hr. An equal volume of water was added and the pH was adjusted to approximately 4 with concentrated HCl. Additional water was added to induce crystallization. After cooling at 0°, the product was collected. Due to the possible formation of *syn* and *anti* isomers, which are both suitable for reduction to the amine but which may have different physical properties or solubility characteristics, purification of the oxime products was usually limited to a single recrystallization. The yields and melting points of the

(15) Melting points were determined in a capillary melting point apparatus and are corrected. Analyses were performed by the microanalytical staff under the direction of Mr. Kermit B. Streeter and Mr. Yung C. Lee.

(16) F. W. Hoover and H. B. Haas, *J. Org. Chem.*, **12**, 501 (1947).

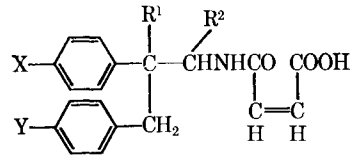
(17) This compound has been prepared in 11% yield from chlorobenzene and chloroacetone by T. M. Patrick, E. T. McBee, and H. B. Haas, *J. Am. Chem. Soc.*, **68**, 1135 (1946), who report bp 85–86° (1 mm), $n^{20}D$ 1.5452.

(18) E. M. Schultz, J. B. Bicking, S. Mickey, and F. S. Crossley, *ibid.*, **75**, 5072 (1953).

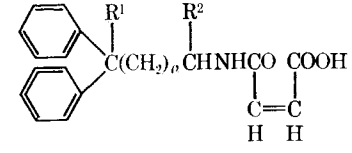
(19) E. P. Kohler, *Am. Chem. J.*, **38**, 511 (1907).

TABLE II

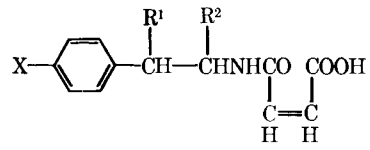
MALEAMIC ACIDS



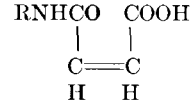
No.	Isomer[a]	X	Y	R[1]	R[2]	Recrystn solvent[b]	Mp, °C	Formula	Calcd,[c] % C	Calcd,[c] % H	Calcd,[c] % N	Found,[c] % C	Found,[c] % H	Found,[c] % N	Dose[e]	Inhib of penicil exer[p] iv	Inhib of penicil exer[p] *po*	Hypocholesterolemic act.[s]
1	*α*	Cl	Cl	H	CH_3	A	209–210	$C_{20}H_{19}Cl_2NO_3$	61.25	4.88	3.57	61.47	4.94	3.54	0.05	+++	+++	++++
2	*β*	Cl	Cl	H	CH_3	B	161–162	$C_{20}H_{19}Cl_2NO_3$	61.25	4.88	3.57	61.26	4.90	3.55	0.05	+	±	++++
3	*α*	Cl	H	H	CH_3	B	187–188	$C_{20}H_{20}ClNO_3$	67.13	5.63	3.92	67.50	5.72	3.90	0.05	+++	++	...
4	*β*	Cl	H	H	CH_3	C	158–160	$C_{20}H_{20}ClNO_3$	67.13	5.63	3.92	67.11	5.78	3.90	0.05	++	±	...
5	*α*	H	Cl	H	CH_3	A	175–176	$C_{20}H_{20}ClNO_3$	67.13	5.63	3.92	67.18	5.66	3.90	0.05	+++	++	...
6	*β*	H	Cl	H	CH_3	B	150–151	$C_{20}H_{20}ClNO_3$	67.13	5.63	3.92	67.30	5.68	3.92	0.1	++	±	...
7	*α*	H	H	H	CH_3	A	181–182	$C_{20}H_{21}NO_3$	74.27	6.55	4.33	74.21	6.57	4.32	0.1	+++	++	++++
8	*β*	H	H	H	CH_3	D	151–152	$C_{20}H_{21}NO_3$	74.27	6.55	4.33	74.55	6.46	4.28	0.1	±	±	+++
9[d]		H	H	H	H	B	114–115	$C_{19}H_{19}NO_3$	73.76	6.19	4.53	73.43	6.03	4.48	0.05	±	±	+
10	*α*	H	H	H	C_2H_5	I	183–185	$C_{21}H_{23}NO_3$	74.75	6.87	4.15	74.59	6.76	4.12				+
11	*β*	H	H	H	C_2H_5	J	136–138	$C_{21}H_{23}NO_3$	74.75	6.87	4.15	74.89	6.62	4.20				++
12	*α*	H	H	H	C_6H_5	J	203–205	$C_{25}H_{23}NO_3$	77.90	6.01	3.63	77.88	5.90	3.58				+
13	*β*	H	H	H	C_6H_5	I	208–211	$C_{25}H_{23}NO_3$	77.90	6.01	3.63	77.66	6.11	3.59				+
14	*α*	H	H	H	$C_6H_5CH_2$	I	207–209	$C_{26}H_{25}NO_3$	78.17	6.31	3.51	77.96	6.28	3.52				+
15	*β*	H	H	H	$C_6H_5CH_2$	I	168–170	$C_{26}H_{25}NO_3$	78.17	6.31	3.51	78.10	6.36	3.49				+
16		H	H	C_2H_5	CH_3	I	162–164	$C_{22}H_{25}NO_3$	75.18	7.17	3.99	75.44	7.26	4.02				++++
17		H	H	$C_6H_5CH_2$	CH_3	I	171–173	$C_{27}H_{27}NO_3$	78.42	6.58	3.34	78.56	6.44	3.37				++++
18		H	H	C_6H_5	CH_3	B	168–172	$C_{26}H_{25}NO_3$	78.17	6.31	3.51	78.32	6.48	3.44				+++



No.	Amine precursor ref	*n*	R	R[2]											
19	*e*	0	H	CH_3	E	206–207	$C_{19}H_{19}NO_3$	73.76	6.19	4.53	74.01	6.26	4.56	0.05	±	+[q]	++++
20	*f*	0	CH_3	CH_3	A	184–185	$C_{20}H_{21}NO_3$	74.28	6.55	4.33	74.32	6.57	4.31	0.05	±	±	+++
21		0	n-C_4H_9	CH_3	A	171–172	$C_{23}H_{27}NO_3$	75.59	7.45	3.83	75.69	7.45	3.83	0.05		±	++
22	*g*	0	CH_3	n-C_4H_9	A	170–171	$C_{23}H_{27}NO_3$	75.59	7.45	3.83	75.50	7.46	3.78	0.05		±	++
23	*h*	1	H	CH_3	F	113–114	$C_{20}H_{21}NO_3$	74.28	6.55	4.33	74.26	6.50	4.33	0.05	+	±	+
24		1	H	n-C_3H_7	F	125–126	$C_{22}H_{25}NO_3$	75.18	7.17	3.99	75.18	7.08	4.02	0.05		±	++
25		1	H	t-C_4H_9	A	192–193	$C_{23}H_{27}NO_3$	75.59	7.45	3.83	75.31	7.37	3.83	0.05	±	±[q]	+
26		1	H	c-C_6H_{11}	A	202–203	$C_{25}H_{25}NO_3$	76.64	7.47	3.58	76.73	7.49	3.59				+



	Amine precursor ref	X	R¹	R₂											
27	*i*	H	H	H	B	132–133	$C_{12}H_{13}NO_3$	65.75	5.98	6.39	65.64	6.04	6.38	0.1	±	±[r]	+
28	*i*	H	H	CH_3	B	124–125	$C_{13}H_{15}NO_3$	66.93	6.48	6.01	67.19	6.61	6.04	0.05	±	±[q]	+++
29	*j*	H	H	$C_6H_5CH_2$	B	161–162	$C_{19}H_{19}NO_3$	73.76	6.19	4.53	73.68	6.06	4.53	0.25	+		+
30	*k*	H	H	C_6H_5	A	164–165	$C_{18}H_{17}NO_3$	73.20	5.80	4.74	73.50	5.80	4.71	0.05	±		+
31		H	$(C_6H_5)_2CH$	CH_3	J	205–207	$C_{26}H_{25}NO_3$	78.17	6.31	3.51	78.49	6.28	3.69				+++
32		*n*-C_4H_9O	*i*-C_3H_7	CH_3	F	117–118	$C_{20}H_{29}NO_4$	69.15	8.41	4.03	69.33	8.36	4.03	0.05	±	±	+



	R												
33	$C_6H_5CH_2$	B	134–135[l]	$C_{11}H_{11}NO_3$	64.38	5.40	6.83	64.13	5.36	6.74			+
34	$C_6H_5CH_2CH_2CH(n\text{-}C_3H_7)$–	G	101–102	$C_{16}H_{21}NO_3$	69.79	7.69	5.09	69.88	7.61	5.07	0.05	±	+
35	$(C_6H_5CH_2)_2CHCH(CH_3)$–	F	142–143	$C_{21}H_{23}NO_3$	74.75	6.87	4.15	74.77	6.89	4.13	0.05	+	++
36	$C_{10}H_7CH_2CH(CH_3)$–[m,n]	A	162–163	$C_{17}H_{17}NO_3$	72.06	6.05	4.95	72.08	6.20	4.94	0.05	±[q]	+++
37	$C_{10}H_7CH(n\text{-}C_4H_9)$–[m]	H	153–154	$C_{19}H_{21}NO_3$	73.29	6.80	4.50	73.19	6.93	4.48	0.25	++	+

Miscellaneous Compounds

	Compd				
38	*d*-N-[3-(*p*-Chlorophenyl)-1-methyl-2-phenylpropyl]maleamic acid α isomer[a]	0.05	++	±	
39	N-(2,3-Diphenyl-1-methylpropyl)-N-methylmaleamic acid	0.1		±	0
40	N-[2,3-Bis(*p*-chlorophenyl)-1-methylpropyl]fumaramic acid α isomer[a]				++
41	N-(2,3-Diphenyl-1-methylpropyl)succinamic acid α isomer[a]				0

[a] The isomer designation assigned to the amic acid is the same as applied to the individual amine isomer from which it is derived. [b] A = ethanol, B = 2-propanol, C = methanol–water, D = benzene, E = acetone (digestion), F = benzene–hexane, G = ether–benzene, H = 2-propanol–water, I = acetonitrile, J = acetic acid. [c] The percentage of chlorine found for **1**–**3**, **5**, and **6** is as follows: **1**, 17.78 (calcd 18.08); **2**, 17.87 (calcd 18.08); **3**, 9.93 (calcd 9.91); **5**, 10.13 (calcd 9.91); **6**, 10.08 (calcd 9.91). [d] J. von Braun, O. Bayer, and L. Cassel, *Chem. Ber.*, **60**, 2602 (1927); the present authors reduced the precursor nitrile with $LiAlH_4$ by the method of L. H. Amundson and L. S. Nelson, *J. Am. Chem. Soc.*, **73**, 242 (1951). [e] J. Levy, P. Galais, and D. Abragan [*Bull. Soc. Chim. France*, **43**, 868 (1928)] prepared the amine by reduction of the oxime (Na–alcohol). The present authors prepared the amine by the Leuckart reaction with the corresponding ketone. [f] H. E. Zaugg, M. Friefelder, and B. W. Horrom, *J. Org. Chem.*, **15**, 1191 (1950). The present authors used the Leuckart reaction and the corresponding ketone to prepare the amine. [g] Reference 24b. [h] J. H. Burckhalter and S. H. Johnson, Jr., *J. Am. Chem. Soc.*, **73**, 4830 (1951). [i] Commercially available. [j] C. F. Koelsch, *J. Am. Chem. Soc.*, **67**, 1718 (1945). [k] R. Leuckart and H. Janssen, *Chem. Ber.*, **22**, 1409 (1889). [l] G. Piutti, *Gazz. Chim. Ital.*, **26I**, 438 (1896), reports mp 138°. [m] $C_{10}H_7$ = 1-naphthyl. [n] For intermediate amine preparation, see L. Vargha and Z. Gyorffy, *Chem. Abstr.*, **42**, 1219*h* (1948). [o] The dose is represented as a fraction of an arbitrary "full dose" which for oral (*po*) administration represents a dose of 30 mg/kg and for intravenous administration (iv) represents 30 mg/kg priming dose and 25 mg/kg/hr sustaining dose given by constant infusion. [p] Test data are presented as the per cent inhibition of penicillin excretion in the drug phase compared to the amount excreted in the untreated control phase; activity is indicated as follows: <25% = ±, 25–50% = +, 50–75% = ++, >75% = +++. Probenecid (*p*-(N,N-dipropylsulfamoyl)benzoic acid), used clinically for inhibition of penicillin excretion, at 0.5 dose has an activity of +++ iv and *po*. [q] Dose level = 0.1. [r] Dose level = 0.25. [s] Testing was carried out essentially by the procedure of ref 4. Compounds were administered to rats at a level of 0.2% in the diet. Hypocholesterolemic activity, measured by plasma cholesterol decrease compared to untreated controls, is scored as follows: inactive = 0, <10% = +, 10–19% = ++, 20–29% = +++, 30% and greater = ++++.

products actually used in the succeeding hydrogenation step are recorded in Table I.

Amine Synthesis by Catalytic Hydrogenation of Oximes.—The oxime was dissolved or suspended in 4 vol. of ethanol, and Raney nickel (one tablespoon per 100 g of oxime) was added. Hydrogenation was carried out at an initial pressure of 40 psi at room temperature and the theoretical amount of hydrogen was taken up in 2–12 hr. The catalyst was removed by filtration and the alcohol solution was worked up as described for the individual amines.

1-Ethyl-2,3-diphenylpropylamine. α Isomer.—Catalytic reduction of the oxime of 1,2-diphenyl-3-pentanone (110 g) was carried out by the general procedure and the solvent was evaporated under reduced pressure. Ether (200 ml), benzene (200 ml), and water (300 ml) were added to the residue and the mixture was made acid to congo red paper by addition of concentrated HCl. A crystalline hydrochloride salt separated and was collected and washed with ether. This was designated as the α isomer. The mother liquor and washings (two phases) were reserved for isolation of the β isomer. The hydrochloride salt was recrystallized from toluene and then ethanol to yield 16.5 g of the hydrochloride salt of the pure α isomer, mp 218–220°.

Anal. Calcd for $C_{17}H_{21}N \cdot HCl$: C, 74.02; H, 8.04; N, 5.08. Found: C, 74.04; H, 8.03; N, 5.04.

β Isomer.—The mother liquor and washings from the hydrochloride of the α isomer were made alkaline (NaOH); the solvent layer was removed and evaporated to yield a noncrystalline residue of 40.6 g. This was dissolved in 40 ml of ethyl alcohol and a hot solution of 16.1 g (0.17 mole) of oxalic acid in 80 ml of ethanol was added. After cooling the mixture to 5°, a crystalline oxalate salt of the β isomer of the amine was obtained (36.5 g). Recrystallization from acetonitrile and then xylene yielded 15.0 g of oxalate salt of the pure β isomer, mp 151–153°.

Anal. Calcd for $C_{17}H_{21}N \cdot C_2H_2O_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.50; H, 7.04; N, 4.25.

1-Benzyl-2,3-diphenylpropylamine. α Isomer.—The oxime of 1,3,4-triphenyl-2-butanone (213 g, 0.675 mole) was reduced by the general procedure and the solution was evaporated *in vacuo*. Ether (200 ml) and 2 *N* HCl (600 ml) were added to the residue and the crystalline hydrochloride salt which formed was collected. The salt was recrystallized from 95% alcohol (1300 ml) and the crystalline product was designated as the α isomer. The mother liquor was reserved for separation of the β isomer. Additional recrystallization of the hydrochloride salt from 95% alcohol yielded the hydrochloride of the pure α isomer, 46 g, mp 217–219°.

Anal. Calcd for $C_{22}H_{23}N \cdot HCl$: C, 78.20; H, 7.16; N, 4.15. Found: C, 78.29; H, 7.42; N, 4.08.

The pure free amine (α isomer) was obtained by treating the pure hydrochloride salt with alkali, extracting the liberated amine with benzene, and then concentrating *in vacuo*. The residual free amine crystallized, mp 77.5–79°.

β Isomer.—The alcohol filtrate from the α-amine hydrochloride was evaporated and the residue was extracted with boiling toluene (700 ml). The insoluble material (17.4 g) was recrystallized from 600 ml of *t*-butyl alcohol, and 13.9 g of the hydrochloride salt of the β isomer of the amine was obtained, mp 217–219°; melting point of a mixture with the hydrochloride salt of pure α isomer was depressed to 188–209°. The free amine (β isomer) was liberated from the hydrochloride salt in the same way as described for the α isomer. The amine was repeatedly crystallized from hexane until pure β isomer, 7.5 g, mp 80.5–82.5°, was obtained. The melting point of a mixture of approximately equal parts of the α and β isomers of the free amine was depressed to 61–70°.

Anal. Calcd for $C_{22}H_{23}N$: C, 87.66; H, 7.69. Found: C, 87.72; H, 7.83.

2-Benzyl-1-methyl-2-phenylbutylamine. α Isomer. Catalytic reduction of 102 g (0.38 mole) of the oxime of 3-benzyl-3-phenyl-2-pentanone was carried out by the general procedure. The solvent was evaporated, the residue was dissolved in 250 ml of ether, and the amine was extracted into 250 ml of dilute HCl. Alkali was added and the amine was extracted with fresh ether. The ether extract was concentrated and a solution of 76.5 g (0.36 mole) of 3,5-dinitrobenzoic acid in 150 ml of isopropyl alcohol was added to the residue of 88.7 g (0.35 mole) of amine. A dinitrobenzoate salt separated which was recrystallized from ethanol to constant melting point of 170.5–172.5° (44.5 g). Although the amine moiety of this salt can exist in two racemic modifications, no other well-defined isomer was isolated. The compound isolated was assigned the α designation.

Anal. Calcd for $C_{18}H_{23}N \cdot C_7H_4N_2O_6$: C, 64.50; H, 5.85; N, 9.03. Found: C, 64.42; H, 5.69; N, 8.93.

1,2,3-Triphenylpropylamine. α Isomer.—The solution obtained from the reduction of 87 g (0.289 mole) of the oxime of 1,2,3-triphenyl-1-propanone by the general procedure was concentrated and the resulting oily residue was dissolved in 200 ml of ether. A small amount of insoluble matter was discarded and 200 ml of benzene and 400 ml of 0.5 *N* HCl were added. A crystalline hydrochloride salt was obtained (63.1 g, mp 230–241°) which was recrystallized from 480 ml of alcohol. The resulting amine hydrochloride obtained in two crops (43.5 g, mp 243–260°) was treated with KOH and the free amine was extracted with benzene. Concentration of the benzene extract yielded 35.2 g of crystalline residue, mp 55–87°. Recrystallization of the residue from hexane gave 18.4 g of amine which was assigned the α designation, mp 92–97°. The mother liquor was set aside for isolation of the β isomer. Two more recrystallizations from hexane yielded the pure α isomer, mp 99–101°.

Anal. Calcd for $C_{21}H_{21}N$: C, 87.76; H, 7.37; N, 4.87. Found: C, 87.89; H, 7.59; N, 4.84.

β Isomer.—The hexane mother liquor from the first crystallization of the free base of the α isomer was concentrated and the residue was dissolved in 35 ml of absolute ethyl alcohol. To this was added a solution of 19 g of *p*-toluenesulfonic acid monohydrate in 100 ml of alcohol. The product was allowed to crystallize at 20° for 1 hr and was then collected; mp 232–251°. After being recrystallized three times from *n*-butyl alcohol, approximately 10 g of the pure *p*-toluenesulfonate salt of the β isomer was obtained, mp 264–266°.

Anal. Calcd for $C_{21}H_{21}N \cdot C_7H_8O_3S$: C, 73.17; H, 6.36; N, 3.05. Found: C, 72.86; H, 6.53; N, 3.03.

The *p*-toluenesulfonate salt of the α isomer of the amine had mp 232–234° and the melting point of a mixture with the β isomer showed a marked depression to 216–238°.

2-Benzyl-2,3-diphenyl-1-methylpropylamine.—The solution obtained from the catalytic reduction of 82.5 g of 3-benzyl-3,4-diphenyl-2-butanone oxime by the general procedure was concentrated to yield the amine as an oil. Distillation yielded a main fraction, bp 211–214° (0.9 mm) (44.7 g). Analyses indicated that further purification was necessary. The picrate proved to be a satisfactory salt and 24.0 g (0.076 mole) of the distilled amine dissolved in 50 ml of acetonitrile was added to a solution of 17.6 g (0.077 mole) of picric acid in 50 ml of the same solvent. Successive recrystallization of the salt from acetonitrile gave 27.2 g of pure picrate, mp 200–202°.

Anal. Calcd for $C_{23}H_{25}N \cdot C_6H_3N_3O_7$: C, 63.97; H, 5.18; N, 10.29. Found: C, 63.99; H, 5.21; N, 10.31.

1-Methyl-2,3,3-triphenylpropylamine. α Isomer.—The oxime of 3,4,4-triphenyl-2-butanone (117 g, 0.372 mole) was reduced by catalytic hydrogenation as described in the general reduction procedure. The amine product was converted to its hydrochloride by addition of an ethanolic HCl solution. The solution was concentrated to remove the alcohol and the residue was crystallized from 275 ml of toluene. Amine hydrochloride, 106.5 g, mp 221–232°, was obtained. After fractional crystallization from toluene and isopropyl alcohol, 24.9 g of pure amine hydrochloride, mp 247–250°, was obtained which was assigned the α designation. No other clearly defined isomer was obtained. The amine hydrochloride was converted to the free amine with aqueous alkali and recrystallized from methylcyclohexane to yield 15 g of pure amine which has a dual melting point. After its first melting point of 117–119°, the melt could be resolidified and a second melting point of 126–128° was obtained.

Anal. Calcd for $C_{22}H_{23}N$: C, 87.66; H, 7.69; N, 4.65. Found: C, 87.45; H, 7.62; N, 4.62.

1-Methyl-2,2,3-triphenylpropylamine.—The solution obtained after catalytic reduction of the oxime of 3,3,4-triphenyl-2-butanone (40.0 g) was concentrated under reduced pressure and 7.7 g of the amine was obtained as an oil. This was used for the preparation of the maleamic acid without further purification.

Amine Synthesis by the Leuckart Reaction on Ketones.—A mixture of the ketone (0.5 mole) and formamide (2.0 moles) was heated under a downward condenser at 170° for 14 hr. Formic acid (about 164 ml) was added in small portions to maintain the vapors above the reaction mixture in an acidic condition. The cooled mixture then was extracted with benzene and the solvent was evaporated. The residue, the N-formyl derivative of the amine, was hydrolyzed by refluxing with concentrated HCl

(65 ml) for 8 hr. Details for isolating the products are presented under the headings of the pertinent amines.

2,3-Bis(*p*-chlorophenyl)-1-methylpropylamine Hydrochloride. α Isomer.—3,4-Bis(*p*-chlorophenyl)-2-butanone (139 g, 0.48 mole) was submitted to a Leuckart reaction in the manner described. After hydrolysis of the formamido intermediate, the acid was decanted and the residue was extracted with boiling water (300 ml) to remove the remaining HCl. The residue then was extracted again with boiling water (300 ml) and the hot mixture was filtered by suction to remove a first crop of the less soluble α isomer. When the mixture was cooled to 20°, a second crop of the α isomer separated. This was harvested and added to the first crop. The filtrate (F) was reserved for isolation of the β isomer. The combined α isomer was crystallized from 2-propanol–water (1:3) to obtain the pure α isomer (29 g, 18%) as the hydrochloride, mp >265°.

Anal. Calcd for $C_{16}H_{17}Cl_2N \cdot HCl$: C, 58.11; H, 5.50; N, 4.24. Found: C, 58.32; H, 5.53; N, 4.22.

β Isomer.—The oily filtrate (F) from the α isomer was diluted with water until the oil dissolved and then extracted with ether. The ether was discarded. The aqueous layer was made basic with 20% NaOH and again extracted with ether. After the ether extract had been dried (K_2CO_3), it was acidified by the addition of alcoholic HCl (6 *N*). The precipitated hydrochloride of the β isomer was collected and crystallized from 2-propanol. The yield was 65 g (41%), mp 184–186°.

Anal. Calcd for $C_{16}H_{17}Cl_2N \cdot HCl$: C, 58.11; H, 5.50; N, 4.24. Found: C, 58.18; H, 5.91; N, 3.93.

2-(*p*-Chlorophenyl)-1-methyl-3-phenylpropylamine Hydrochloride. α Isomer.—The reaction mixture from a Leuckart reaction on 3-(*p*-chlorophenyl)-4-phenyl-2-butanone (80 g) was added, with stirring, to water (250 ml). A purple oil, a mixture of the hydrochlorides of the α and β forms of the amines, separated. This material has the peculiar property of being almost insoluble in cold water but soluble in ether. The oil was extracted with ether. The ether solution, which now contained all of the product, was extracted 25–30 times with 250-ml portions of water. Each water extract was made basic (20% NaOH) and serially extracted with two 250-ml portions of ether. There was thus obtained, on combining the two portions of ether extracts, about 500 ml of ether containing all of the basic products. This ether solution was dried (K_2CO_3) and acidified with alcoholic HCl (6 *N*). After chilling at 5° for 16 hr, the α form (7 g) separated and was collected. The filtrate (F) was reserved for isolation of the β isomer. The solid was crystallized from water to obtain pure α isomer HCl (4.8 g), mp 250°.

Anal. Calcd for $C_{16}H_{18}ClN \cdot HCl$: C, 64.87; H, 6.46; N, 4.73. Found: C, 65.20; H, 6.50; N, 4.71.

β Isomer.—The ether filtrate (F) from the α isomer was evaporated. The residue (51 g) was crystallized from benzene–hexane (3:2) to obtain the β isomer (39 g), mp 196–198°.

Anal. Calcd for $C_{16}H_{18}ClN \cdot HCl$: C, 64.87; H, 6.46; N, 4.73. Found: C, 64.63; H, 6.46; N, 4.70.

3-(*p*-Chlorophenyl)-1-methyl-2-phenylpropylamine Hydrochloride. α Isomer.—The hydrolysis mixture of a Leuckart reaction on 4-(*p*-chlorophenyl)-3-phenyl-2-butanone (113 g, 0.435 mole) was added to water (*ca.* 200 ml). A water-insoluble precipitate remained undissolved. This solid was collected and washed with water. The filtrate and washings (F) containing the β isomer were reserved. The crude solid was crystallized from water to obtain the pure α isomer hydrochloride, mp 290–292°.

Anal. Calcd for $C_{16}H_{18}ClN \cdot HCl$: C, 64.87; H, 6.46; N, 4.73. Found: C, 64.93; H, 6.56; N, 4.70.

β Isomer.—The aqueous filtrate (F) from the crude α isomer was extracted with ether and made basic (20% NaOH). The oil that separated was extracted with ether. The ether extract was dried (K_2CO_3) and acidified with alcoholic HCl (6 *N*). The precipitate was collected and crystallized from isopropyl alcohol to obtain the pure β isomer, mp 179–180°.

Anal. Calcd for $C_{16}H_{18}ClN \cdot HCl$: C, 64.87; H, 6.46; N, 4.73. Found: C, 64.92; H, 6.56; N, 4.76.

2,3-Diphenyl-1-methylpropylamine Hydrochloride. α Isomer.—The hydrolysis mixture of the formamido intermediate obtained from the Leuckart reaction on 3,4-diphenyl-2-butanone[18] was made basic by addition of 20% NaOH and extracted with ether. The dried ether solution was evaporated and the residue was distilled to obtain the mixture of isomeric amines, bp 120–122° (0.5 mm). The distillate, 137 g, was suspended in water (200 ml) and concentrated HCl was added at 15° until a lasting precipitate just formed. The mixture was heated to 80° and then cooled to 20°. A crude solid (51 g, mp 210–228°), designated α isomer, separated and was collected. The filtrate was reserved for isolation of the β isomer. The crude α isomer was crystallized from water to obtain 32 g of pure α isomer hydrochloride,[20] mp 247–248°.

Anal. Calcd for $C_{16}H_{19}N \cdot HCl$: N, 5.35; Cl, 13.55. Found: N, 5.33; Cl, 13.56.

β Isomer.—The filtrate which was reserved for isolation of the β isomer was kept at 20° while concentrated HCl (*ca.* 20 ml) was added until a lasting precipitate formed. The mixture was heated at 80° and then cooled to 5°. The solid that separated was collected and crystallized from 2-propanol to obtain the pure β isomer hydrochloride, mp 161–162°.

Anal. Calcd for $C_{16}H_{19}N \cdot HCl$: C, 73.40; H, 7.70: N, 5.35. Found: C, 73.28; H, 7.18; N, 5.31.

1-(2,2-Diphenylethyl)butylamine.—1,1-Diphenyl-3-hexanone was submitted to a Leuckart reaction in the manner described by the general procedure. After hydrolysis of the intermediate formamido derivative with HCl, the reaction mixture was made basic (20% NaOH) and extracted with ether. The dried ether solution was evaporated and the residue was distilled to obtain the desired amine, bp 145–150° (0.3 mm).

In a similar manner, using the designated ketone, the following amines were prepared.

2,2-Dimethyl-1-(2,2-diphenylethyl)propylamine, bp 128–130° (0.2 mm), mp 78–80° (from hexane), from 1,1-diphenyl-4,4-dimethyl-3-pentanone.[19] *Anal.* Calcd for $C_{11}H_{25}N$: C, 85.34; H, 9.42; N, 5.25. Found: C, 85.40; H, 9.51; N, 5.21.

1-Cyclohexyl-3,3-diphenylpropylamine, bp 180–181° (0.5 mm), from 1-cyclohexyl-3,3-diphenyl-1-propanone.

1-(2-Phenethyl)butylamine, bp 142° (25 mm), from 1-phenyl-3-hexanone.[21]

1-(1-Naphthyl)pentylamine, bp 119–123° (0.1 mm), from 1-(1-naphthyl)-1-pentanone.[22]

2-Benzyl-1-methyl-3-phenylpropylamine, bp 193–198° (15 mm), from 3 benzyl-4-phenyl-2-butanone.[23] Neither the hydrochloride, benzamide, nor phenylthiourea of this amine could be obtained in crystalline form.

2-(*p*-Butoxyphenyl)-1,3-dimethylbutylamine Hydrochloride.—The amine (bp 125–130° (0.3 mm)) obtained from 3-(*p*-butoxyphenyl)-4-methyl-2-pentanone by the Leuckart reaction was dissolved in ether and precipitated as the hydrochloride by addition of alcoholic HCl. After repeated crystallizations from acetone, a pure isomer melting at 174–175° was obtained as the hydrochloride. Although two racemic modifications are possible, no other well-defined isomer was obtained.

Anal. Calcd for $C_{16}H_{27}NO$: C, 67.22; H, 9.87; N, 4.90. Found: C, 67.36; H, 9.78; N, 4.89.

2,3-Diphenyl-1-methylpropylmethylamine.—3,4-Diphenyl-2-butanone[18] (0.38 mole) and N-methylformamide (1.5 moles) reacted under Leuckart conditions to yield 55 g (61%) of the amine, bp 120–122° (0.2 mm). The base (54 g) was converted to the hydrochloride by dissolving it in ether (250 ml) and acidifying with 3 *N* ethanolic HCl. The solid hydrochloride (56 g), mp 163–169°, was crystallized repeatedly from methanol to obtain a hydrochloride (16 g), mp 191–192°, which appeared to be a pure isomer. The second of the two possible isomers was not isolated.

Anal. Calcd for $C_{17}H_{21}N \cdot HCl$: C, 74.03; H, 8.04; Cl, 12.86. Found: C, 74.18; H, 8.07; Cl, 12.76.

2,2-Diphenyl-1-methylhexylamine.—By the method of Pickard, *et al.*,[24] 2,2-diphenylhexanenitrile[25] was treated with methylmagnesium bromide to yield the crude ketimine of 3,3-diphenyl-2-heptanone. This was hydrogenated in methanol over prereduced Adams catalyst to yield product, bp 115–120° (0.2 mm). The **phenylthiourea derivative** melted at 191–192°.

---

(20) E. Ishiwata and K. Suzuki [*J. Pharm. Soc. Japan*, **71**, 1272 (1951); *Chem. Abstr.*, **46**, 5591*i* (1952)] prepared the amine by reduction of the corresponding oxime (Na–EtOH) but report only a hydrochloride salt, mp 249°.

(21) C. Harries and P. Bromberger, *Chem. Ber.*, **35**, 3089 (1902), reduced 1-phenyl-2-hexen-3-one with NaHg. The present authors used catalytic hydrogenation over Pd in ethanol.

(22) L. G. Nunn and H. R. Henze, *J. Org. Chem.*, **12**, 540 (1947).

(23) H. Leuchs, A. Heller, and A. Hoffmann, *Chem. Ber.*, **62**, 87 (1929).

(24) (a) P. L. Pickard and D. J. Vaughn, *J. Am. Chem. Soc.*, **72**, 876 (1950); (b) P. L. Pickard and E. F. Engles, *ibid.*, **75**, 2148 (1953).

(25) J. Hoch and M. Lecocq, *Compt. Rend.*, **245**, 73 (1957); *Chem. Abstr.*, **52**, 1967*g* (1958).

Anal. Calcd for $C_{20}H_{27}N_2S$: C, 77.56; H, 7.54; N, 6.96. Found: C, 77.33; H, 7.82; N, 6.99.

Maleamic Acids. General Preparative Procedure.—A solution of the amine in 10–15 vol. of ether was mixed slowly with a solution of maleic anhydride (20% *M* excess) in 10 vol. of ether. (Those amines isolated as acid addition salts were suspended in dilute NaOH and the free amine was extracted into ether. The ether extract was dried and evaporated to a volume 10–15 times that of the amine.) Formation of a crystalline product began almost immediately. The mixture then was stirred for 2 hr and the product was collected. Yields were usually better than 70–80% and frequently were almost quantitative. The purity of the products so obtained was such that in many instances the melting point was unchanged by subsequent crystallization. Recrystallization solvents, physical constants, and analytical data are shown in Table II.

***dl*-N-[3-(*p*-Chlorophenyl)-1-methyl-2-phenylpropyl]maleamic Acid. α Isomer (38).**—*dl*-N-[3-(*p*-Chlorophenyl)-1-methyl-2-phenylpropyl]maleamic acid α isomer (**5**, Table II) (50 g, 0.14 mole) was added to quinine (45.2 g, 0.14 mole) in boiling acetone (325 ml). The solid that separated on cooling to 5° was crystallized repeatedly from acetone to obtain 10 g of the quinine salt, mp 127–130°. The salt was decomposed in dilute NaOH, and the aqueous mixture was extracted with ether and acidified with HCl. The solid that separated was crystallized from benzene to obtain the dextrorotatory compound, $[\alpha]^{25}D$ +41.33° (*c* 1, ethanol).

Anal. Calcd for $C_{20}H_{20}ClNO_3$: C, 67.13; H, 5.63; N, 3.92. Found: C, 67.44; H, 5.79; N, 3.92.

N-(2,3-Diphenyl-1-methylpropyl)-N-methylmaleamic Acid (39).—2,3-Diphenyl-1-methylpropylmethylamine in ether was added to an ether solution of an equimolar amount of maleic anhydride. No precipitate formed and on evaporation of the ether a thin oil remained. This was induced to solidify by trituration with hexane and crystallized from benzene–hexane to obtain the pure maleamic acid, mp 100–101°.

Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.59; H, 6.78; N, 5.14.

Ethyl N-[2,3-Bis(*p*-chlorophenyl)-1-methylpropyl]fumaramate. α Isomer.—A solution of 9.76 g (0.06 mole) of ethyl fumaryl chloride[26] in 20 ml of benzene was added over a 5-min period to a solution of 17.67 g (0.06 mole) of the α isomer of 2,3-bis(*p*-chlorophenyl)-1-methylpropylamine in 90 ml of benzene. Triethylamine (7.5 ml) was then added and the solution was stirred for 1 hr. Ether (100 ml) was added and the solution was extracted successively with 1 *N* HCl, water, saturated $NaHCO_3$, and water. The organic phase was dried and concentrated to yield 19.8 g (78.7%) of product, mp 99–108°. For purification for analysis, a sample was dissolved in excess ether and the solution was concentrated to a small volume for crystallization, mp 112–115°.

(26) R. Anschütz, *Ann. Chem.*, **461**, 155 (1928).

Anal. Calcd for $C_{22}H_{23}Cl_2NO_3$: C, 62.86; H, 5.52; N, 3.33. Found: C, 62.86; H, 5.80; N, 3.27.

N-[2,3-Bis(*p*-chlorophenyl)-1-methylpropyl]fumaramic Acid. α Isomer (40).—A solution of 2.77 g (0.0494 mole) of KOH in 5.4 ml of water was added to a mixture of 19.8 g (0.0472 mole) of ethyl N-[2,3-bis(*p*-chlorophenyl)-1-methylpropyl]fumaramate and 50 ml of alcohol. The mixture was stirred until all of the ester dissolved and the solution was then allowed to stand for 18 hr. Water (50 ml) was added and the mixture was concentrated *in vacuo* to about 30 ml. The oily residue was suspended in 200 ml of 50% aqueous methanol and extracted once with 200 ml of ether. The clear aqueous layer was separated, cooled to 5°, and acidified with 2.5 *N* HCl. An oil separated which was extracted with two 200-ml portions of ether. The extract was dried and the ether was evaporated under reduced pressure. The residue was dissolved in 200 ml of benzene and the product began crystallizing almost immediately. The product, 15.6 g, was recrystallized from 300 ml of chloroform, and 13.2 g (71.3%) of **40** was obtained, mp 99.5–110°.

Anal. Calcd for $C_{20}H_{19}Cl_2NO_3$: C, 61.23; H, 4.88; N, 3.57. Found: C, 61.33; H, 5.11; N, 3.44.

N-(2,3-Diphenyl-1-methylpropyl)succinamic Acid. α Isomer (41).—A benzene solution of 2,3-diphenyl-1-methylpropylamine (α isomer) was added to a benzene solution of an equimolar amount of succinic anhydride. After 16 hr, a small amount of solid had separated. This was harvested and the benzene filtrate was evaporated to dryness. The residual oil was dissolved in $NaHCO_3$ solution. Upon acidification a rapidly solidifying oil separated. The combined solid was dried and crystallized from benzene–hexane to obtain pure **41**, mp 117–119°.

Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.57; H, 7.18; N, 4.29.

Influence of the Method of Conversion of Ketones to Amines on the Ratio of α to β Isomers.—3,4-Bis(*p*-chlorophenyl)-2-butanone oxime (50 g, 0.162 mole) in ethanol (150 ml) was hydrogenated at 80° over Raney nickel (10 g wet weight) in a stainless steel pressure vessel at an initial hydrogen pressure of 800 psi during a period of 5 hr. Removal of catalyst and solvent left a residue of 48 g of a mixture of the α and β forms of the amine. The ratio of the α:β isomer was established by conversion of the crude mixture of isomers to the corresponding maleamic acid (α and β forms) by the general procedure. From 48 g (0.162 mole) of the mixture of amines, there was obtained 43 g (67%) of a mixture of the α and β isomers of N-[2,3-bis(*p*-chlorophenyl)-1-methylpropyl]maleamic acid. The mixture was refluxed with 2-propanol (6 ml/g) for 1–1.5 hr. The insoluble α isomer of the maleamic acid (34 g, 53%), mp 209–210°, was collected from the hot mixture. The filtrate was reheated and allowed to cool slowly to 5°. The precipitate (7.34 g, 11%) was the β isomer, mp 160–161°. The yields of the maleamic acid isomers are indicative of the ratio of isomers in the crude amine. Comparison of these yields with the amounts of α and β isomers of this amine obtained by the Leuckart reaction described earlier shows the effect of the synthetic procedure upon the isomeric composition of the product.