in the presence of 40 g. of 10% palladium-charcoal at normal pressure and at about 40°. After 17.5 l. of hydrogen was absorbed in about 35 min., the catalyst was filtered and the filtrate was evaporated *in vacuo*. The semisolid residue was triturated with methanol to give 164 g. of dihydrochloride. The base, obtained by treating a solution of the dihydrochloride with an excess of sodium hydroxide, melted at 128–129° after recrystallization from toluene. This product could also be obtained in 90% yield by direct debenzylation of compound **8** in diluted 2-propanol.

1-Benzyl-4-pyrrolidino-4-piperidinecarboxylic Acid Dihydrochloride Hydrate.—A solution of 71.5 g. (0.5 mole) of 1-benzyl-4-pyrrolidino-4-piperidinecarboxamide in 1 l. of concentrated hydrochloric acid was refluxed for 26 hr. The reaction mixture was evaporated to dryness under diminished pressure. The solid residue was recrystallized first from a mixture of hydrochloric acid and water (1:1), then from water to give 29 g. (15.3%) of material, m.p. 260–262°.

Anal. Calcd. for $C_{17}H_{24}N_2O_2 \cdot 2HCl \cdot H_2O$: neut. equiv. (base), 189.5; neut. equiv. (acid), 126.3; Cl, 18.69; N, 7.37; H_2O, 4.75. Found: neut. equiv. (base), 194; neut. equiv. (acid), 129; Cl, 18.74; N, 7.52; H_2O 3.76.

1-γ-(4-Fluorobenzoylpropyl)-4-piperidino-4-piperidinecarboxamide (25).—A mixture of 5.6 g. (0.03 mole) of γ-chloro-4-fluorobutyrophenone,[12] 4.1 g. (0.02 mole) of 4-piperidino-4-piperidinecarboxamide, 6.4 g. (0.065 mole) of sodium carbonate, and some crystals of potassium iodide in 175 ml. toluene was refluxed with stirring for 48 hr. The mixture was cooled, and 50 ml. of water was added. The organic phase was separated, dried over potassium carbonate, filtered, and evaporated. The solid residue was washed with ether to yield 4 g. (54.9%) of the above compound, m.p. 124.5-126°. This product was converted to its **hydrochloride** which, after trituration in boiling 2-propanol, melted at 261-263°.

1-(3-Carboxamido-3,3-diphenylpropyl)-4-piperidino-4-piperidinecarboxamide (31).—A solution of 4.3 g. (0.01 mole) of compound **30** in 60 ml. of 90% sulfuric acid was heated for 3 hr. at 100°. After allowing to cool to 50°, the reaction mixture was poured onto an excess of ammonium hydroxide and crushed ice. The precipitated solid was extracted into chloroform. After drying the extract, the solvent was removed by distillation leaving a solid, which, after recrystallization from a mixture of acetone and diisopropyl ether, gave 2.8 g. of compound **31**.

(12) C. van de Westeringh, B. Hermans, F. Raeymaekers, and C. Van der Eycken, *Ind. Chim. Belge*, 1073 (1960).

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Diphenylpropylamine Derivatives. I. N-Substituted 3,3-Diphenylpropylamines

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Reductive condensation of 3,3-diphenylpropionaldehyde with primary amines such as 3,3-diphenylpropylamine with ketones leads to N-substituted 3,3-diphenylpropylamine derivatives. 3,3-Diphenylpropionaldehyde could be obtained in 60–65% yield by the Rosenmund reaction. Reductive condensation with basic ketones resulted in more readily soluble 3,3-diphenylpropylamine derivatives. The coronary dilator action of some of the products was determined.

The search for new synthetic analgesics has led to the preparation of diphenylpropylamine derivatives. A comprehensive survey of this work has been given.[1] Lindner[2a,b] and Kochsiek, *et al.*,[2c] reported on a new therapeutic action of one member of this group. The compound, N-(3-phenyl-2-propyl)-3,3-diphenylpropylamine[2d] (I), is a coronary dilator of prolonged action.

$$(C_6H_5)_2CH(CH_2)_2NHCH(CH_3)CH_2C_6H_5$$
I

Ehrhart described the preparation of I and its analogs[3] and used various diarylalkyl groups as N-substituents of 2-amino-1-phenylpropane, emphasizing interest in the N-phenyl-2-aminopropane section of the molecule.

We have studied certain structural changes of I by retaining intact the 3,3-diphenylpropyl group and varying only the other substituent on the nitrogen atom. The preparation of these compounds was based on the assumption that it might be easiest to form a carbon–nitrogen bond by reductive condensation in the final step of the synthesis. These compounds can be synthesized from 3,3-diphenylpropionaldehyde (II) *via* 3,3-diphenylpropylamine (III).

Although III can be prepared satisfactorily by the method described in the literature,[4] the methods given for the preparation of II result in poor yields. According to Bockmühl, *et al.*,[5] II can be obtained by allowing diphenylmethane to react with chloroacetal in the presence of sodium. There was no mention of the yield; in repeating these directions, we were just about able to identify II in the reaction product.

In their work concerning the reaction of mercury chloroaldehydes with halogen compounds Curtin and Hurwitz described the preparation of II from mercury chloroacetaldehyde and diphenylchloromethane in the presence of tin tetrachloride.[6] A 37% yield was obtained under extreme anhydrous conditions.

We have succeeded in obtaining distilled II by the Rosenmund method in a 60–65% yield from 3,3-diphenylpropionic acid which is easily accessible. The

(1) P. A. J. Janssen, "Synthetic Analgesics," Pergamon Press, London, 1960, Part 1.

(2) (a) E. Lindner, *Arzneimittel-Forsch.*, **10**, 569, 573 (1960); (b) H. H. Schöne and E. Lindner, *ibid.*, **10**, 583 (1960); (c) K. Kochsiek, H. J. Bretschneider, and F. Scheler, *ibid.*, **10**, 583 (1960); (d) Prenylamine®.

(3) G. Ehrhart, *Arch. Pharm.*, **295**, 196 (1962).

(4) S. K. Freeman, W. F. Ringk, and P. E. Spoerri, *J. Am. Chem. Soc.*, **69**, 858 (1947).

(5) M. Bockmühl, G. Ehrhart, O. Eisleb, and L. Stein, U. S. Patent 2,446,552 (1948).

(6) D. Y. Curtin and M. J. Hurwitz, *J. Am. Chem. Soc.*, **74**, 5381 (1952).

synthesis involved the reaction of II with primary amines or the reaction of III with various ketones. The catalytic hydrogenation was followed by, or carried out simultaneously with the condensation.

$$\underset{\text{II}}{(C_6H_5)_2CHCH_2CHO} + H_2NR \xrightarrow{H_2} (C_6H_5)_2CH(CH_2)_2NHR + H_2O$$

$$\underset{\text{III}}{(C_6H_5)_2CHCH_2CH_2NH_2} + R_1R_2CO \xrightarrow{H_2} (C_6H_5)_2CH(CH_2)_2NHCHR_1R_2 + H_2O$$

The reductive condensation of II with primary amines resulted in a poor yield of the corresponding secondary amine, as the amine in the system induced aldolization of II. The nitrogen-free aldol was separated from the reaction mixture.

$$2\text{II} \rightarrow (C_6H_5)_2CHCH_2CHOH\underset{\substack{|\\ CHO}}{C}HCH(C_6H_5)_2$$

By reductive condensation of 3,3-diphenylpropionaldehyde with primary amines, secondary amines with primary carbon atoms on the nitrogen were prepared. The reductive condensation of III with ketones gave an excellent yield of the desired secondary amine. By an appropriate choice of the ketone component the following structural changes were performed.

(a) Variation of the distance between the nitrogen atom and the aromatic ring occurred by substitution of 1-phenylethyl and 1-phenyl-3-butyl for 1-phenyl-2-propyl.

(b) The methyl group on the α-carbon atom was substituted by longer alkyl radicals (1-phenylpropyl and 1-phenyl-2-butyl). A poorer yield was obtained after reductive condensation of these derivatives, due probably to steric hindrance.

(c) Hydroxy and alkoxy substituents were introduced into the aromatic ring.

(d) The aralkyl radical was substituted by a cycloalkyl condensed benzene ring in the case of N-indanyl. Here good yields were obtained.

(e) Some cycloalkyl derivatives were also prepared.

All these compounds and their salts are but poorly soluble in water. To improve water solubility basic ketones were used for the reductive condensation. 4-(4-Dimethylaminophenyl)-2-butanone was used to form the aralkyl substituent and 1-ethyl-4-piperidone for the formation of a substituent similar to the cyclohexyl group; 2-(2-dimethylaminoethyl)indanone and tropinone were used in the reductive condensation step.

Some representative ketones containing basic groups were also prepared, with phenolic ethers as the basic group in the molecule. Vasodilators with similar functional groups are known, *e.g.*, 3,4-bis-(4-diethylaminoethoxyphenyl)hexane. The preparation of such compounds from ketones with free phenolic hydroxyls was carried out according to the method of Rohmann and Meisel.[7] Products substituted with the latter basic group formed salts with better solubility in water. However, the yield of these products after reductive condensation was lower than that of the analogous ketones without basic groups.

(7) C. Rohmann and D. Meisel, *Arch. Pharm.*, **294**, 538 (1961).

These substances were tested for coronary dilator activity in cats by the Langendorff method[8] with cat blood as perfusing fluid and in dogs by the Morawitz canule.[9] These tests have shown that the coronary dilator action depends on the N-substituted 3,3-diphenylpropylamine structure. In cats the average increase in coronary flow caused by 100 γ of I was 56.8% and the same doses of compounds **1**, **5**, and **7** of Table I and **4** of Table II produced average increases of 64.7, 56, 42, and 51%, respectively. In dogs 1 mg./kg. of I raised coronary flow by 11.7% and reduced calculated coronary vascular resistance by 23.4%. The same doses of compounds **1** and **5** increased coronary flow by 12 and 11.4%, and reduced resistance by 21 and 22%, respectively (average values of 5–10 experiments). Although the N-substituted groups were structurally different (see tables), the compounds displayed a coronary dilator action similar to that of I.

Clinical trials have shown that N-1-phenylethyl-3,3-diphenylpropylamine hydrochloride has a coronary dilator effect comparable to that of I [N-(3-phenyl-2-propyl)-3,3-diphenylpropylamine].[10]

Experimental[11]

3,3-Diphenylpropionaldehyde by the Rosenmund Reaction.—3,3-Diphenylpropionyl chloride (38.09 g.) was obtained from the reaction of 41.60 g. of 3,3-diphenylpropionic acid with 42.4 ml. of thionyl chloride. The product distilled at 152–154° (0.4 mm.). It was dissolved in 208 ml. of anhydrous xylene, and 2.4 ml. of quinoline–sulfur catalyst poison and 16.5 g. of 5% Pd–$BaSO_4$ catalyst were added. The apparatus was provided with a stirrer, reflux condenser, and hydrogen inlet. Reaction time was 4 hr. at the boiling point of the solution. The catalyst was filtered off and the filtrate was shaken with 10% Na_2CO_3. On acidification 2.53 g. of 3,3-diphenylpropionic acid was obtained. Evaporation of the xylene solution furnished 30.13 g. of solvent-free residue, which when distilled gave a main fraction, b.p. 143–145° (1.4 mm.), 20.71-g. (63.5%) yield, which solidified on cooling; m.p. of dinitrophenylhydrazone 176–177° (lit.[6] corrected value 177–178°).

N-3,4-Dimethoxyphenethyl-3,3-diphenylpropylamine Hydrochloride.—3,3-Diphenylpropionaldehyde (11.75 g.) and 10.12 g. of 3,4-dimethoxyphenethylamine were heated on the water bath for 20 min. The melt was dissolved in 100 ml. of anhydrous alcohol and hydrogenated at atmospheric pressure in the presence of Pd–C catalyst. Hydrogen uptake was below the calculated value. The catalyst was filtered off, and the filtrate was evaporated to dryness. The residue (17.85 g.) was dissolved in 100 ml. of ether, and a small quantity of undissolved substance was filtered off. On addition of anhydrous ethanolic hydrogen chloride, 15.33 g. of a substance precipitated which melted between 110 and 150°. When recrystallized from a mixture of 30 ml. of anhydrous ethanol and 60 ml. of ethyl acetate, 5.92 g. of a substance melting at 186–187° was obtained, the melting point remaining unchanged after repeated recrystallization.

Anal. Calcd. for $C_{25}H_{30}ClNO_2$: C, 72.88; H, 7.34; N, 3.4. Found: C, 72.74; H, 7.06; N, 3.39.

Reaction of Diphenylpropionaldehyde with Phenethylamine.—3,3-Diphenylpropionaldehyde (10.50 g.) and 6.1 g. of phenethylamine were heated for 20 min. over a water bath in 100 ml. of anhydrous ethanol. The solution was transferred to a hydrogenation vessel. A considerably smaller hydrogen uptake than calculated was observed. The solution was filtered while warm. After cooling, 3.15 g. of substance precipitated which when recrystallized from alcohol melted at 127°.

Anal. Calcd. for $C_{30}H_{28}O_2$ (5,5-diphenyl-2-diphenylmethyl-3-hydroxypentanal): C, 85.68; H, 6.71. Found: C, 85.47; H, 6.56.

(8) O. Langendorff, *Pflugers Arch. Ges. Physiol.*, **61**, 219 (1895).

(9) P. Morawitz and A. Zahn, *Zentr. Physiol.*, **26**, 465 (1912).

(10) Personal communications of Professor Gottsegen, National Institute of Cardiology, Budapest.

(11) Melting points are corrected.

TABLE I

N-SUBSTITUTED 3,3-DIPHENYLPROPYLAMINE DERIVATIVES FROM 3,3-DIPHENYLPROPYLAMINE WITH KETONES

No.	Ketone	B.p. of amine, °C. (mm.)	% yield of distilled base	Salt forming acid	% yield of salt	M.p., °C.	Empirical formula	Analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	Acetophenone	191 (0.15)	80.5	HCl	81.5	206	$C_{23}H_{26}ClN$	78.50	7.45	4.02	78.34	7.50	3.90
2	Propiophenone	215–217 (0.6)	70.5	HCl	80.5	212–213	$C_{24}H_{28}ClN$	78.77	7.71	3.83	79.05	7.69	3.89
3	1-Phenyl-2-butanone	...	...	Maleic acid	69.5[a]	131–132	$C_{29}H_{33}NO_4$	75.95	7.03		75.65	7.05	
4	4-Phenyl-2-butanone	201–202 (0.08)	85.5	Maleic acid	92.5	135	$C_{29}H_{33}NO_4$	75.95	7.03		75.95	6.98	
5	4-(4-Hydroxyphenyl)-2-butanone	119–122[b]	80	Maleic acid	86	125	$C_{29}H_{33}NO_5$	73.24	6.99		73.28	6.87	
6	4-(4-Hydroxy-3-methoxyphenyl)-2-butanone	112[c]	83	Maleic acid	89.5	122–125	$C_{30}H_{35}NO_6$	71.26	6.98		71.11	6.98	
7	Cyclohexanone	160–162 (0.15)	91.5	Maleic acid	98	173	$C_{25}H_{31}NO_4$	73.33	7.63	3.42	73.29	7.51	3.44
8	1-Indanone	...	...	HCl	82[a]	201	$C_{24}H_{26}ClN$	79.20	7.20		79.11	7.09	
9	3-Phenyl-1-indanone	...	...	Maleic acid	70[a]	213	$C_{34}H_{33}NO_4$	78.59	6.40		78.63	6.74	

[a] Yield of salt formation from the crude base. [b] M.p. *Anal.* Calcd. for $C_{25}H_{28}NO$: N, 3.90. Found: N, 3.85. [c] M.p. *Anal.* Calcd. for $C_{26}H_{31}NO_2$: C, 80.17; H, 8.02; N, 3.60. Found: C, 80.02; H, 7.96; N, 3.58.

TABLE II

N-SUBSTITUTED 3,3-DIPHENYLPROPYLAMINES FROM 3,3-DIPHENYLPROPYLAMINE WITH BASIC KETONES

No.	Ketone	B.p. of amine, °C. (mm.)	% yield of distilled base	Salt forming acid	% yield of salt	M.p., °C.	Empirical formula	Analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	4-(4-Diethylaminoethoxyphenyl)-2-butanone	246–249 (0.1)	75	2Maleic acid	93	120–122	$C_{39}H_{50}N_2O_9$	67.80	7.30	4.06	67.80	6.98	4.08
2	4-(4-Piperidinoethoxyphenyl)-2-butanone	...	...	2HCl	72[a]	226	$C_{32}H_{44}Cl_2N_2O$	70.83	7.94	5.16	70.89	8.00	5.33
3	4-(Diethylaminoethoxy)-acetophenone	264–268 (0.6)	63	2HCl	87	223	$C_{29}H_{40}Cl_2N_2O$	69.16	8.01		69.15	8.13	
4	4-(4-Dimethylaminophenyl)-2-butanone	...	...	1Maleic acid	71[b]	149–150	$C_{29}H_{38}N_2O_4$	72.77	8.00	5.85	72.74	7.69	5.86
5	1-Ethyl-4-piperidone	210–214 (0.6)	55	2HCl	75	310–312	$C_{22}H_{32}Cl_2N_2 \cdot H_2O$	63.91	8.29	6.78	63.96	8.07	6.54
6	2-(2-Dimethylaminoethyl)indanone	...	...	2HCl	63[a]	218	$C_{28}H_{36}Cl_2N_2$			5.94			5.65
7	Tropinone	214–218 (0.15)	45	2HCl	[c]	284[d]	$C_{23}H_{32}Cl_2N_2$	67.80	7.92	6.88	68.03	8.03	6.82

[a] Yield of salt formation from the crude base. [b] Yield of salt formation from the crude base, calculated for the crude salt; there was considerable loss at recrystallization. [c] *endo* and *exo* isomers can be precipitated with a 68% yield, m.p. 185–192°. [d] One of the isomers crystallized from ethyl alcohol.

The aldol was filtered off and the filtrate was evaporated. On addition of alcoholic HCl, 2.77 g. of hydrochloride salt was obtained. The substance which crystallized from the mother liquor had no sharp melting point. It was recrystallized from 25% anhydrous ethanol and 75% ethyl acetate, giving 1.78 g. of phenethylamine hydrochloride, m.p. 222°. From the mother liquor a crystalline substance was precipitated with water which was found to be N-phenethyl-3,3-diphenylpropylamine hydrochloride, m.p. 213–214°.

Anal. Calcd. for $C_{23}H_{26}ClN$: C, 78.49; H, 7.45; N, 3.98. Found: C, 78.72; H, 7.55; N, 3.91.

General Method for the Reductive Condensation of 3,3-Diphenylpropylamine and Ketones.—Equivalent quantities of 3,3-diphenylpropylamine and ketone were hydrogenated in methanol in the presence of Pd–C catalyst at temperatures between 50–60° and at 5–12 atm. At the end of the reaction the catalyst was filtered off, and the solvent evaporated. The base was purified either by distillation *in vacuo* or by direct salt formation.

The two compounds containing free phenolic hydroxyls (Table I, **5** and **6**) were obtained in crystalline form after treatment with ethyl acetate. Similar reactions were carried out with basic ketones. The ketones for the reaction were prepared as follows.

4-(4-Piperidinoethoxyphenyl)-2-butanone.—A mixture of 32.8 g. (0.2 mole) of 4-(4-hydroxyphenyl)-2-butanone, 70 g. of powdered K_2CO_3, 1 ml. of water, 300 ml. of acetone, and 15 ml. of methanol were weighed into a round-bottomed flask fitted with a Soxhlet extractor; 37.0 g. (about 0.2 mole) of piperidinoethyl chloride hydrochloride was added. The solution was boiled under reflux for 20 hr., after which the bulk of the solvent was distilled off and the residue was poured into 500 ml. of water. The oily substance, insoluble in water, was taken up with ether and washed with an aqueous solution of 8 g. of NaOH. Evaporation of the ether left 46.96 g. of substance which when distilled gave 44.77 g. boiling at 201–202° (0.8 mm.). A small quantity of this distillate was used to form the hydrochloride salt, melting at 136°.

Anal. Calcd. for $C_{17}H_{26}ClNO_2$: C, 65.48; H, 8.41; N, 4.49. Found: C, 65.77; H, 8.57; N, 4.39.

4-(4-Diethylaminoethoxyphenyl)-2-butanone.—As diethylaminoethyl chloride hydrochloride is more soluble, a shorter reaction time was sufficient and the acetone used contained no methyl alcohol. The main fraction was collected at 174–176° (0.6 mm.). Starting from 0.2 mole, 43.7 g. (83%) of the substance was obtained. The hydrochloride salt melted at 108–109°.

Anal. Calcd. for $C_{16}H_{26}ClNO_2$: N, 4.67. Found: N, 4.53.

4-(Diethylaminoethoxy)acetophenone.—The method used was the same as above. The product boiled at 152° (0.6 mm.). Its hydrochloride salt had m.p. 149–150°.

Anal. Calcd. for $C_{14}H_{21}ClNO_2$: N, 5.16. Found: N, 5.06.

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