TABLE VIII

LOCAL ANESTHETIC ACTIVITY[a]

No.	Concentration of test material, % 0.05	0.10	0.25	0.50	Carbonyl frequency, μ	pK_a of parent acid
1*t*	75	81	...	100	5.9	7.23
2*t*	70	85	...	96	5.91	7.51
5*t*	0	10	90	96	5.81	6.77
1*c*	...	30	...	36	5.8	5.94
2*c*	0	2	...	10[b]	5.8	6.12
5*c*	...	21	66	68	5.8	5.35
Lidocaine[c]	63	92	95	95	...	...

[a] Calculated as 100 − % response (see text). [b] The value is at 0.3% concentration, 0.5% irritated the eye. [c] The local anesthetic activity of lidocaine at 0.01% is 17%, and at 1% is 100%.

the methoxy group decreases the potency as in **2***c*. A more sensitive method, ionization constants, was used to determine minor changes in electron density. In the *trans* series, the p*K*a values of the α-phenylcinnamic acids parallel with the carbonyl stretching frequency of the amino esters and are directly proportional to the local anesthetic activity. In the *cis* series, the pK_a values of the acids are inversely proportional to the local anesthetic activity. The activity of **1***t* and **2***t* is approximately the same as that of lidocaine when tested by the corneal reflex method.

Experimental[15]

β-Dimethylaminoethyl α-Phenyl-*trans*-cinnamates.—The acid chlorides were prepared by heating the acids[6] with a 10% excess of thionyl chloride in refluxing benzene for 30 min. One drop of pyridine per gram of acid was added to the reaction mixture. The solvent and excess thionyl chloride were removed in a rotatory evaporator. The acid chloride was dissolved in hexane and the evaporation repeated. In 3 cases (**2***t*, **5***t*, and **9***t*) the acid chlorides were recrystallized from hexane and analyzed (Table I). This was found to be unnecessary since the crude acid chlorides afforded good yields of the esters. In most cases the acid chloride in benzene, when treated with 1 mole of the amino alcohol at room temperature, afforded the solid ester hydrochloride which was collected by filtration. With **2***t*, **7***t*, and **9***t*, 2 moles of the amino alcohol were allowed to react with the acid chloride and the solid amino alcohol hydrochloride was removed by filtration. The filtrate was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness *in vacuo*. An ether solution of the free ester was treated with dry hydrogen chloride to give the ester hydrochloride, which was collected by filtration. When β-dimethylaminoethyl α-*p*-nitrophenyl-*trans*-*p*-nitrocinnamate was crystallized from 95% ethanol, it was converted to the ethyl ester, m.p. 166–167°, confirmed by its identity with an authentic sample prepared from the acid chloride and ethanol.

Data on these preparations are in Table I and the analytical data are in Table III.

β-Dimethylaminoethyl α-Phenyl-*cis*-cinnamates.—The optimum conditions for conversion of the *cis* acids[6] to acid chlorides are outlined in Table II, the analyses are in Table III. After removal of solvent and excess thionyl chloride, the crude acid chloride or mixture of acid chlorides in ether was treated with 2 moles of the amino alcohol. After removal of the aminoethanol hydrochloride and conversion to the ester hydrochloride as described above for **2***t*, **7***t*, and **9***t*, the *cis* amino esters were purified by repeated fractional crystallization. The higher melting isomer (*trans* except for **2***c*) crystallized first. The purity of the *cis* isomer was followed by disappearance of the infrared carbonyl absorption band associated with the *trans* isomer. Further proof of identity and purity was obtained from the ultraviolet spectra. The spectra of the *cis* ester hydrochlorides were in all cases nearly identical with those of the corresponding *cis* acids but markedly different from the *trans* ester hydrochlorides or acids. Since the carboxy and the carbalkoxy groups are essentially equivalent chromophores, the same curves for the esters and the acids were taken as proof of identity of the esters.

Isomerization Studies on α-Phenyl-*cis*-*p*-methoxycinnamic Acid.—Reaction of the *cis* acid in benzene at 80 and 25° afforded exclusively the *trans* acid chloride as evidenced by the infrared spectra and melting point of the ester product. The *cis* acid (0.25 g., 0.99 mmole) was stirred with thionyl chloride (0.144 g., 0.09 ml., 1.2 mmoles) and a catalytic amount of pyridine (0.5 drop) in ether for 60 to 90 min. in a bath maintained at −10 to −5°, or at −60 to −55° and treated with the amino alcohol after removal of excess thionyl chloride. At the lower temperature only the free *trans* acid was obtained; when carried out at −10 to −5°, a mixture of acid chlorides and later amino ester hydrochlorides containing approximately 55% *cis* and 45% *trans* was obtained. These values were estimated from the relative intensities of the two infrared carbonyl absorption bands in the acid chlorides and amino ester hydrochlorides (Table IV).

Acknowledgment.—The authors are indebted to Dr. Violette Sutherland and Mr. Masa Rikimaru for their help and guidance in the design and interpretation of the pharmacological studies. The technical assistance of Misses Sharon Sousa and Sui Mei Lui is also acknowledged.

(15) Melting points were taken on a Fisher-Johns melting point block and are corrected. Microanalyses were performed in the microanalytical laboratory, Department of Chemistry, University of California, Berkeley, Calif.

4-Substituted Piperidines. I. Derivatives of 4-*t*-Amino-4-piperidinecarboxamides

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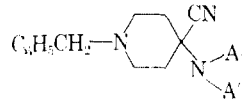
A number of derivatives of 4-*t*-amino-4-piperidinecarboxamides have been prepared. The pharmacological screening has shown that 1-(γ-butyrophenone) derivatives may be classified as neuroleptic agents, whereas the 1-(α,α-diphenyl-γ-butyronitrile) derivatives constitute analgesic agents. The latter compounds elicit relatively minor addiction symptoms.

Our interest in therapeutic agents derived from piperidine led us to prepare a large number of 4,4-disubstituted and 4-substituted piperidine derivatives. The purpose of this first paper is to describe compounds of the general formula I, in which NAA′ represents a nitrile or a carboxamide group. L is much less clearly defined and can represent a number of different substituent groups.

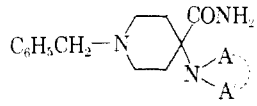
TABLE I



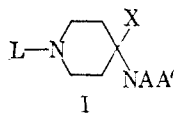
Compd.	N(A)A'	Method	Yield,[a] %	M.p., °C.	Formula	Calcd., % N	Calcd., % Cl⁻	Calcd., Neut. equiv.	Found, % N	Found, % Cl⁻	Found, Neut. equiv.
1	$N(CH_3)_2$	A	83	107–109	$C_{15}H_{21}N_3$	17.27	...	122	17.12	...	122
2	C_4H_8N[b]	A	87	87.6–89	$C_{17}H_{23}N_3$	15.60	...	135	15.66	...	132
3	$C_5H_{10}N$[c]	A	84	104.6–105.6	$C_{18}H_{25}N_3$	14.83	...	142	14.60	...	140
4	$C_6H_{12}N$[d]	B	66	149–153 dec.	$C_{19}H_{27}N_3 \cdot 2\ HCl$	11.34	19.13	185	10.76	19.07	189
5	C_4H_8NO[e]	A	58	117–117.8	$C_{17}H_{23}N_3O$	14.73	...	285[f]	14.71	...	285

[a] Most of the indicated yields in this and subsequent tables are based on a single run and they do not necessarily reflect the optimum attainable. [b] Pyrrolidino. [c] Piperidino. [d] Hexamethyleneimino. [e] Morpholino. [f] The morpholino substituent is too weak to be determined by titration. Footnotes *b*, *c*, *d*, and *e* apply also to Tables II, III, V, and VI.

TABLE II



Compd.	N(A)A'	Yield, %	M.p., °C.	Formula	Calcd., % N	Calcd., Neut. equiv.	Found, % N	Found, Neut. equiv.
6	$N(CH_3)_2$	80	122–123.8	$C_{15}H_{23}N_3O$	16.08	131	15.86	133
7	C_4H_8N	74	124–126	$C_{17}H_{25}N_3O$	14.62	143.5	14.86	145.5
8	$C_5H_{10}N$	91	147–148	$C_{18}H_{27}N_3O$	13.94	150.5	13.99	152
9	$C_6H_{12}N$	51	110–111	$C_{19}H_{29}N_3O$	13.32	158	13.46	159
10	C_4H_8NO	24	132–134.2	$C_{17}H_{25}N_3O_2$	13.85	151.5	13.84	153



I

As the chemistry is virtually the same for all of the compounds involved, regardless of the nature of L, this paper will deal only with the most important and representative species of this series; for the related compounds, reference is made to the patent literature.[1]

Chemistry.—The first step of the preparation of all compounds involves the synthesis of 4-cyano-4-cycloalkyleneimino(or dialkylamino-)piperidine derivatives. These compounds belong to the class of α-amino nitriles, which in general can be prepared conveniently by reaction of an appropriately chosen ketone or aldehyde with a secondary amine and hydrogen cyanide under a variety of reaction conditions.

Two major modifications of this reaction are described in the literature. In method A, the Tieman–Strecker synthesis, the ketone is treated with hydrogen cyanide and the secondary amine, either in a one-step reaction or in two successive steps, whereas in method B, the Knoevenagel synthesis, an adduct of the ketone and sodium bisulfite is formed first; this is then allowed to react with the amine and hydrogen cyanide, again in a one- or two-step reaction sequence.

Although the preparation of such amino nitriles derived from cyclo ketones such as cyclohexanone is very well known, the use of heterocyclic ketones, as far as we know, has never been described. We found that starting from N-substituted 4-piperidones, in some cases, fair to excellent yields of the desired amino nitriles could be obtained. The N-benzyl derivative was chosen as starting compound since, in subsequent reactions, this blocking group can be removed easily by hydrogenolysis, thus allowing for the subsequent introduction of other substituents in this position.

In most cases, method A or B gave fair to good yields. However, of the cyclic imines, the hexamethyleneimine derivative could be obtained only by method B; for 2-methylpiperidine, the reaction failed altogether. Of the dialkylamines, only dimethylamine gave good results. The reaction failed for the higher homologs, although several modifications of both methods were applied. We can offer no simple explanation for our failures, except in the case of 2-methylpiperidine, where steric factors might play a role.

In Table I the compounds prepared by either of the two methods are indicated. In the Experimental part each of the methods is illustrated by one example.

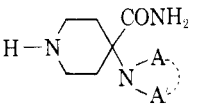
The chemical properties of α-amino nitriles in general are determined to a large extent by the fact that they bear an electropositive and an electronegative group on the same carbon atom, and the properties of this class of compounds are rather unique.[2] For the nitriles discussed here, the situation is even more complicated, due to the presence of another amine function in the molecule. It was therefore not unexpected that the preparation of even rather simple derivatives of these compounds could not always be accomplished by straight forward reactions.

In the literature we found no example of the direct alcoholysis of an α-amino nitrile (derived from a ketone) to the corresponding ester, and upon applying this reaction to our compounds, the desired esters could not be obtained. We then tried to prepare the esters *via* the free acids and acid chlorides. Although the

(1) P. A. J. Janssen, U. S. Patents 3,041,344 and 3,080,366 (1963).

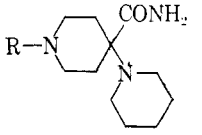
(2) For a more detailed discussion of this class of compounds, see V. Migrdichian in "The Chemistry of Organic Cyanogen Compounds," Reinhold Publishing Corp., New York, N. Y., 1947, covering the literature up to 1947, and a review by P. Van Daele, *Mededel. Vlaam. Chem. Ver.*, **23**, 163 (1961), covering more recent literature.

TABLE III



Compd.	NAA′	Yield, %	M.p., °C.	Formula	Calcd., % N	Calcd., % Cl⁻	Calcd., % Neut. equiv.	Found, % N	Found, % Cl⁻	Found, % Neut. equiv.
11	$N(CH_3)_2$	90	119–121	$C_8H_{17}N_3O$	24.54	...	85.5	24.65	...	86
12	C_4H_8N	85	141–142	$C_{10}H_{19}N_3O$	21.30	...	99	21.30	...	99
13	$C_5H_{10}N$	90	128–129	$C_{11}H_{21}N_3O$	19.89	...	105.5	19.75	...	106
	$C_5H_{10}N$	81	299–301	$C_{11}H_{21}N_3O \cdot 2HCl$	14.80	24.95	142	14.63	24.90	144
14	$C_6H_{12}N$	80	111–118 dec.	$C_{12}H_{23}N_3O$	18.66	...	112.5	18.49	...	114
15	C_4H_8NO	82	188–191	$C_{10}H_{19}N_3O_2$	19.70	...	107	19.83	...	109

TABLE IV



Compd.	R	Yield, %	M.p., °C.	Formula	Calcd., % N	Calcd., % Neut. equiv.	Found, % N	Found, % Neut. equiv.
16	CH_3	45	128–136 dec.	$C_{12}H_{23}N_3O \cdot H_2O$[a]	17.27	121.5	17.35	122
17	$C_6H_5(CH_2)_2$	23	157–159	$C_{19}H_{29}N_3O$	13.32	157.5	13.39	157.5
18	$C_6H_5(CH_2)_3$	45.5	96–98	$C_{20}H_{31}N_3O$	12.76	164.5	12.31	165
19	$C_6H_5O(CH_2)_2$	54.5	98–100	$C_{19}H_{29}N_3O_2$	12.68	165.5	12.41	167.5
20	$C_6H_5O(CH_2)_3$	43.5	97–98	$C_{20}H_{31}N_3O_2$	12.16	172.5	12.25	174.5
21	$4\text{-}FC_6H_4O(CH_2)_3$	13.8	114–115	$C_{20}H_{30}FN_3O_2$	11.56	181.5	11.43	185
22	$C_9H_9O_2$[b]	44.5	130–132	$C_{20}H_{29}N_3O_3$	11.69	179.5	11.56	180
	$C_9H_9O_2$[b]	...	281–283	$C_{20}H_{29}N_3O_3 \cdot 2HCl$	...	216	...	214.5[c]

[a] *Anal.* Calcd.: H_2O, 7.4. Found: H_2O, 7.5 (Karl Fischer). [b] 2-(1,4-Benzodioxanyl)methyl. [c] *Anal.* Calcd.: Cl^-, 16.41. Found: Cl^-, 16.26.

hydrolysis of α-amino nitriles to the corresponding acids has been described repeatedly, results indicate that this reaction proceeds very erratically. In particular, a successful hydrolysis of α-*t*-amino nitriles derived from ketones has been described only once.[3] It was therefore again not surprising that both acid and alkaline hydrolysis failed in our hands in all but one case. Although the acid so obtained, 1-benzyl-4-carboxy-4-(1-pyrrolidino)piperidine dihydrochloride hydrate, reacted with thionyl chloride, we could not isolate the acid chloride. Reaction of alcohol with the crude reaction product did not yield the desired ester.

On the other hand, it was found that treatment of the nitriles with 90% sulfuric acid for about 10 min. at 100°, yielded, in most cases, the corresponding primary carboxamides in essentially quantitative yields. They are represented in Table II, and in the Experimental part the preparation of one of them is given. Compounds of Table II could be catalytically debenzylated in excellent yields. In Table III the compounds prepared in this manner are surveyed.

Finally, the introduction of a variety of substituents could be accomplished in most cases in good yields by reaction of the secondary amines with the appropriate halides in toluene or in methyl isobutyl ketone in the presence of sodium carbonate or other proton-accepting agents. A large number of such compounds has been prepared, but for the sake of brevity only a limited number is represented in Tables IV, V, and VI. For related compounds reference is made to the patent literature.[1] In the Experimental part this alkylation reaction is illustrated by one example, and the hydrolysis of **30** into the corresponding carboxamide **31** is described.

Pharmacology.—The pharmacological screening gave the following results. The N-benzyl derivatives (Table II) and the nor compounds (Table III) were found to be devoid of CNS-depressant activity. The N-methyl (Table IV, **16**), the N-aralkyl (Table IV, **17** and **18**) and the N-aryloxyalkyl derivatives (Table IV, **19–21**) of 4-piperidino-4-piperidinecarboxamide were also found to be devoid of CNS-depressant activity. The benzodioxanyl derivative (Table IV, **22**) showed some slight adrenolytic activity.

Neuroleptic activity was found for all 4-amino compounds derived from butyrophenone. Several compounds of this type, most of them not mentioned here (see, however, ref. 1), have been prepared and, as in the haloperidol series, the highest activity was found in the 4-fluoro compounds (Table V, **23–27**). Of the modifications in the 4-position, the activity in this series decreased in the order, piperidine > hexamethyleneimine > pyrrolidine > morpholine > dimethylamine, the most active compound being **25** (Floropipamide).[4] For this reason the latter was selected for a comparative pharmacological study with other neuroleptic agents. The results of this study have been published elsewhere.[5]

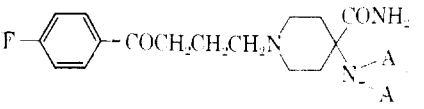
Finally, the compounds derived from α,α-diphenylbutyronitrile (Table VI, **28–34**) were shown to exhibit potent analgesic activity. The most potent species is **30**, where NAA′ is piperidine. This compound

(3) R. B. Moffett, *J. Org. Chem.*, **14**, 862 (1949).

(4) Dipiperon®.

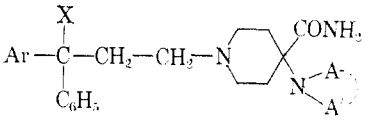
(5) P. A. J. Janssen, *Arzneimittel-Forsch.*, **11**, 819, 932 (1961).

TABLE V



Compd.	N<A,A	Yield, %	M.p., °C.	Formula	Calcd., % N	Calcd., % Cl⁻	Calcd., % Neut. equiv.	Found, % N	Found, % Cl⁻	Found, % Neut. equiv.
23	$N(CH_3)_2$	32	227–228.5 dec.	$C_{18}H_{26}FN_3O_2 \cdot 2HCl$	10.29	17.37	204	10.12	17.09	205.5
24	C_4H_8N	10	237–240 dec.	$C_{20}H_{28}FN_3O_2 \cdot 2HCl$	...	16.33	217	...	16.09	215
25	$C_5H_{10}N$	65	124.5–126	$C_{21}H_{30}FN_3O_2$	11.19	...	187.5	11.13	...	189
	$C_5H_{10}N$	...	255–257 dec.	$C_{21}H_{30}FN_3O_2 \cdot 2HCl$	9.37	15.81	224	9.47	15.95	225
26	$C_6H_{12}N$	39	242–243 dec.	$C_{22}H_{32}FN_3O_2 \cdot 2HCl$	9.09	15.34	231	9.08	15.56	229
27	C_4H_8NO	34	150–151.8	$C_{20}H_{28}FN_3O_3$	11.13	...	377	11.20	...	375

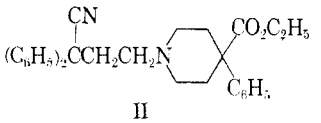
TABLE VI



Compd.	Ar	X	N<A,A	Yield %	M.p., °C.	Formula	Calcd., % N	Calcd., % Cl⁻	Calcd., % Neut. equiv.	Found, % N	Found, % Cl⁻	Found, % Neut. equiv.
28	C_6H_5	CN	$N(CH_3)_2$	28	270–271	$C_{24}H_{30}N_4O \cdot 2HCl$	12.09	15.30	231	...	15.04	232
29	C_6H_5	CN	C_4H_8N[a]	25	159–160	$C_{26}H_{32}N_4O$	13.45	...	208	13.42	...	201
30	C_6H_5	CN	$C_5H_{10}N$	60	149–150	$C_{27}H_{34}N_4O$	13.01	...	216	12.83	...	214
	C_6H_5	CN	$C_5H_{10}N$	...	>290 dec.	$C_{27}H_{34}N_4O \cdot 2HCl$	11.13	14.08	251.5	...	14.40	255
31	C_6H_5	$CONH_2$	$C_5H_{10}N$	62	215–218	$C_{27}H_{36}N_4O_2$	12.49	...	225	12.39	...	228
32	4-F-C_6H_4	CN	$C_5H_{10}N$	20	121–122	$C_{27}H_{33}FN_4O$	12.49	...	224	12.70	...	227
33	C_6H_5	CN	$C_6H_{12}N$	10	289–291 dec.	$C_{28}H_{36}N_4O \cdot 2HCl$	10.83	13.70	258.5	10.63	13.85	255
34	C_6H_5	CN	C_4H_8NO	12	204–205	$C_{26}H_{32}N_4O_2$	12.95	...	434	12.83	...	428

[a] See footnotes *b*, *c*, *d*, and *e*, Table I.

(Piritramide) has a potency of about twice that of morphine. For the other compounds of this series the analgesic activity again decreases in the order piperidine > hexamethyleneimine > pyrrolidine > morpholine > dimethylamine. Piritramide is structurally closely related to diphenoxylate II, which is



II

a potent antidiarrheal agent, devoid of morphine-like activity.[6] Furthermore, it can be considered as structurally related to both the methadone and the pethidine types of analgesics, but for both series it is very unusual for this structure to exhibit analgesic activity.

In view of this unusual structure, the mechanism of the analgesic activity of Piritramide could be different from that of other morphine-like drugs. For this reason this compound was chosen for further pharmacological and clinical investigations. Although the preliminary results suggesting that this compound did not produce physical dependence in dogs[7] could not be confirmed in monkeys, it was found that it elicits relatively minor addiction symptoms. The results of these investigations have been published elsewhere.[8]

Experimental[9,10]

1-Benzyl-4-cyano-4-piperidinopiperidine (3). Method A.—To a stirred solution of 130 g. (2 moles) of potassium cyanide and 243 g. of piperidine hydrochloride in a mixture of 80 ml. of water and 400 ml. of ethanol was added dropwise, 378 g. (2 moles) of 1-benzyl-4-piperidone.[11] After about 1 hr., a solid started to precipitate. The reaction was completed by stirring the mixture for 24 hr. at room temperature. The resulting solid was recrystallized from diisopropyl ether to yield 238 g.

1-Benzyl-4-cyano-4-hexamethyleneiminopiperidine (4). Method B.—To 37.8 g. (0.2 mole) of 1-benzyl-4-piperidone was added with stirring, a solution of 41.6 g. (0.4 mole) of sodium bisulfite in 80 ml. of water at an initial temperature of 0°. An exothermic reaction occurred, and the temperature rose to about 25°. Stirring and cooling were continued for about 30 min. when 24 g. (0.24 mole) of hexamethyleneimine was added dropwise. After stirring the reaction mixture overnight at room temperature, 13 g. (0.2 mole) of finely powdered potassium cyanide was added. After stirring for 2 hr. at room temperature and for 1 hr. at 50–60°, the mixture was cooled again to room temperature. Water (100 ml.) was added and the whole was extracted first with two 700-ml. portions of ether, then with 400 ml. of chloroform. After drying the combined extracts, the reaction product was converted to the dihydrochloride salt by passing dry hydrogen chloride into the solution which was treated with acetone to give 48.9 g. of product.

1-Benzyl-4-piperidino-4-piperidinecarboxamide (8).—A mixture of 14.2 g. (0.05 mole) of 1-benzyl-4-cyano-4-piperidinopiperidine and 40 ml. of 90% sulfuric acid was heated on a steam bath for 10 min. The mixture was allowed to cool to room temperature and poured onto 150 g. of crushed ice. The solution was made alkaline with ammonium hydroxide, and the separated base was extracted with chloroform. After drying the extract and distilling the solvent, the residual oil was triturated with cold acetone to give 13 g. of the carboxamide.

4-Piperidino-4-piperidinecarboxamide Dihydrochloride (13).—A solution of 215 g. (0.7 mole) of 1-benzyl-4-piperidino-4-piperidinecarboxamide in 1500 ml. of 2-propanol, 1000 ml. of water, and 140 ml. of concentrated hydrochloric acid was hydrogenated

(6) P. A. J. Janssen, *J. Med. Pharm. Chem.*, **1**, 299 (1959).
(7) J. La Barre, private communication.
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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**.

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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

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