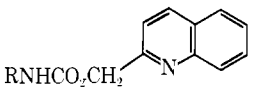
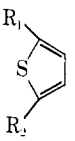
TABLE V
QUINOLINE DERIVATIVES



No.	R	Mp, °C	Crystn solvent[a]	Method[b]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
123	CH_3	94.5–95	B–J	1	$C_{12}H_{12}N_2O_2$	66.65	5.60		66.75	5.70	
124	C_6H_5	129.5–130.5	C–J	1	$C_{17}H_{14}N_2O_2$	73.36	5.07	10.07	73.11	5.13	10.25

[a,b] See footnotes in Table I.

TABLE VI
THIOPHENE DERIVATIVES



No.	R_1	R_2	Mp, °C	Crystn solvent[a]	Method[b]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
125	H	$CH_3NHCONHCH_2$	96.5–97.5	E	1	$C_7H_{10}N_2OS$	49.40	5.92	16.46	49.36	6.00	16.60
126	$CH_3NHCO_2CH_2$	$CH_3NHCO_2CH_2$	89–91	G–B	1	$C_{10}H_{14}N_2O_4S$	46.51	5.42	10.85	46.75	5.54	10.88
127	$C_2H_5NHCO_2CH_2$	$C_2H_5NHCO_2CH_2$	98–100	A–J	1	$C_{12}H_{18}N_2O_4S$	50.35	6.28	9.79	50.40	6.37	9.58

[a,b] See footnotes in Table I.

was prepared from 2,6-bis(chloromethyl)pyridine[24] in 56% yield by the Gabriel method.[25]

6-Methyl-2-pyridinemethanol N-oxide, mp 111–115°, was prepared from 6-methyl-2-pyridinemethanol by the method of Furukawa.[26]

2-Nitro-1,3-benzenedimethanol.—1,3-Dimethoxycarbonyl-2-nitrobenzene[27] was reduced with $NaBH_4$ and $AlCl_3$ in diethyleneglycol dimethyl ether by a general method for the reduction of esters to alcohols in the presence of nitro groups.[28] The light-sensitive 2-nitro-1,3-benzenedimethanol was recrystallized from water to give yellow needles, mp 101.5–102° (32.5% yield).

Anal. Calcd for $C_8H_9NO_4$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.30; H, 5.05; N, 7.74.

3-Methylbenzyl alcohol[29] **and 1,3-benzenedimethanol**[30] were prepared by the reductions of methyl *m*-toluate and dimethyl isophthalate, respectively, with $LiAlH_4$ in tetrahydrofuran solutions.

1,3-Benzenedimethanethiol[31] was prepared from 1,3-benzenedimethanol according to the general procedure of Frank and Smith.[20]

2,5-Thiophenedimethanol, bp 123–125° (0.05 mm), was prepared from thiophene by the method of Griffing and Salisbury.[32]

General Methods for the Preparation of Carbamates and Ureas. Method 1.—A solution of an alcohol, thiol, or amine in an appropriate solvent such as pyridine, benzene, toluene, acetone, or ether was treated with an isocyanate, acyl isocyanate, sulfonyl isocyanate, isothiocyanate, or carbamoyl chloride at temperatures ranging from room temperature to the reflux temperature of the solution for 0.5–108 hr. Reactions using the more volatile isocyanates, such as methyl isocyanate, were conducted in glass pressure bottles.

Method 2.—A solution of an alcohol and potassium *t*-butoxide in *t*-butyl alcohol was treated with an isothiocyanate at room temperature.[33]

Method 3.—A solution of an alcohol in benzene or pyridine was heated under reflux with an acid azide.

Method 4.—Primary carbamates were prepared from the reaction of an alcohol with sodium cyanate and trifluoroacetic acid in methylene chloride.[34]

Method 5.—A monosubstituted urea was prepared by heating an aqueous solution of an amine hydrochloride and KCNO on a steam bath for 45 minutes.[35]

Method 6.—A solution of an amine in a solvent such as benzene or ether was treated with an alkyl or aryl chloroformate in the presence of a base such as pyridine or triethylamine.

Acknowledgment.—The authors are particularly grateful to Dr. Max E. Bierwagen and his staff for all of the pharmacological test results and for helpful comments during the preparation of this manuscript. Thanks are also due to Mr. J. C. Heffernan for technical assistance and to the analytical and spectroscopic departments for their services.

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2-Acylimino-1,1-dimethylphenethylamines and Related Compounds. Anorectic Agents

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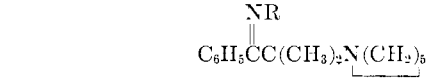
Numerous substituted phenethylamines exhibit central nervous system stimulation and anorectic activity.[1] We found that 1-(2-imino-1,1-dimethyl-2-phenylethyl)-piperidine (I), when administered to mice by the oral route caused significant CNS stimulation and depres-

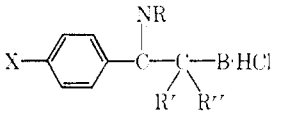


I, R = H
II, R = $COCH_3$

(1) R. A. McLean in "Medicinal Chemistry," A. Burger Ed., Interscience Publishers, Inc., New York, N. Y., 1960, Chapter 29, p 592.

TABLE I

2-ACYLIMINO-1,1-DIMETHYLPHENETHYLAMINES AND RELATED COMPOUNDS



No.	X	R	R′	R″	B[a]	Mp, °C[b]	Formula	Chlorine, % Calcd	Chlorine, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Toxicity in mice, oral LD_{50}, mg/kg	Anorectic activity in mice, oral ED_{50}, mg/kg[c]
1	H	H	CH_3	CH_3	NC_5H_{10}	175–177	$C_{16}H_{25}ClN_2$	13.29	13.08	10.50	10.74	420	70
2	H	$COCH_3$	CH_3	CH_3	NC_5H_{10}	171–173	$C_{17}H_{25}ClN_2O$	11.48	11.57	9.07	9.23	415	10
3	H	$COCH_2Cl$	CH_3	CH_3	NC_5H_{10}	149–150	$C_{18}H_{27}ClN_2O$	10.98	01.00	8.68	8.61	490	130
4	H	$COCH_2C_6H_5$	CH_3	CH_3	NC_5H_{10}	168–170	$C_{23}H_{29}ClN_2O$	9.21	9.23	7.28	7.30	135	23
5	H	$COCH{=}CHC_6H_5$	CH_3	CH_3	NC_5H_{10}	175–176	$C_{23}H_{29}ClN_2O$	8.93	8.72	7.05	6.90	950	[d]
6	H	COC_6H_5	CH_3	CH_3	NC_5H_{10}	185–186	$C_{23}H_{27}ClN_2O$	7.55	7.38	9.56	9.66	705	40
7	H	COC_6H_4-2-Cl	CH_3	CH_3	NC_5H_{10}	192–194	$C_{23}H_{26}Cl_2N_2O$	17.49	17.66	6.91	6.98	560	86
8	H	COC_6H_4-4-Cl	CH_3	CH_3	NC_5H_{10}	193–195	$C_{23}H_{26}Cl_2N_2O$	17.49	17.19	6.91	7.15	675	>50
9	H	SO_2CH_3	CH_3	CH_3	NC_5H_{10}	224–225	$C_{16}H_{25}ClN_2O_2S$	10.29	10.25	8.12	7.91	290	28
10	Cl	COC_6H_5	CH_3	CH_3	NC_5H_{10}	185–187	$C_{23}H_{26}Cl_2N_2O$	17.49	17.14	6.91	6.95	>1200[e]	>100
11	H	$COCH_2C_6H_5$	CH_3	CH_3	$N(CH_3)_2$	118–120	$C_{20}H_{25}ClN_2O \cdot H_2O$[f]	9.77	9.91	7.72	7.59	320	>100
12	H	COC_6H_5	CH_3	CH_3	NC_4H_8O	185–187	$C_{21}H_{23}ClN_2O_2$	9.51	9.47	7.51	7.71	365	11
13	H	$COCH_3$	$-(CH_2)_5-$		NC_5H_{10}	159–161	$C_{20}H_{29}ClN_2O$	10.16	9.90	8.03	7.93	>1135[g]	250
		Related compd, HCl salts											
14		1-(3-Amino-α,α-dimethylphenethyl)piperidine				161–162	$C_{16}H_{28}ClN_3$	13.19	13.50	10.42	10.55	220	>80
15		N-[α-(1-Methyl-1-piperidinoethyl)benzyl]-2-phenylacetamide				252–254	$C_{24}H_{33}ClN_2O$	9.16	9.02	7.21	7.18	[g]	>64[h]
16		N,N,1,1-Tetramethyl-2-phenylethylenediamine				140–141	$C_{12}H_{21}ClN_2$	15.50	15.80	12.25	11.98	390	80
17		2-Methyl-2-piperidinopropiophenone				161–163	$C_{15}H_{22}ClNO$	13.24	13.42	5.23	5.16	560	62
18[i]		β,β-Dimethyl-α-phenyl-1-piperidineethanol				259–260	$C_{15}H_{24}ClNO$	13.11	13.04	5.19	5.18	205	>50
19		4′-Chloro-2-methyl-2-piperidinopropiophenone				193–195	$C_{15}H_{21}Cl_2NO$	23.46	23.48	4.63	4.83	720	92
20		1-(1-Benzoylcyclohexyl)piperidine				195–197	$C_{19}H_{26}ClNO$	11.52	11.35	4.55	4.61	>1900[e]	265

[a] NC_5H_{10} = piperidino and NC_4H_8O = morpholino. [b] These salts were crystallized from the following solvents: **1**, **2**, **7**, **8**, **16**, and **19**, acetonitrile; **3**, **10**, **11**, and **13**, butanone; **4** and **5**, isopropyl alcohol; **6** and **12**, acetonitrile–ether; **9**, **14**, and **18**, ethanol; **16**, first from acetonitrile as a solvate and then from methanol–ether; **17** and **20**, acetone. [c] The ED_{50} for phenmetrazine in this test procedure is 13 mg/kg. The notation >*x* means there was no inhibition of food consumption at dose *x*, the highest level tested. Compd **5** was not tested in mice; it was about one-half as active as phenmetrazine in the dog. [d] LD_{50}. [e] The anhydrous form (mp 144–146°) was obtained by heating at 56° at 2 mm. *Anal.* Calcd Cl, 10.28; N, 8.18. Found: Cl, 10.35; N, 7.99. [f] LD_{50}. The LD_{50} (intravenous) is 82 mg/kg. [g] Not determined. [h] This water-insoluble material was tested as a suspension in 0.25% agar. [i] Obtained by the reaction of the free base of **17** with excess $LiAlH_4$ in ether; base mp 104–105° (hexane), lit.[5] mp 105–106° (base) and 260–261° (HCl salt). [j] LD_{50}. The LD_{50} (intravenous) is 150 mg/kg.

sion of food intake. Treatment of the free base of I (Ia) with acetyl chloride yielded II; the latter showed greater anorectic activity than I. Ia was treated with other acyl chlorides to give some of the compounds listed in Table I. Acyl derivatives of the analogs of I in which the piperidino group was replaced by dimethylamino and morpholino, the modification wherein the two methyl groups are replaced by a pentamethylene linkage, in addition to an acyl derivative of the *p*-chloro analog of I, were prepared. Hydrogenation of I gave the amino compound **14** and the latter was converted to the phenacetylamido derivative **15**. Hydrolysis of I yielded the ketone **17** and reduction of the latter gave the corresponding alcohol **18**.

The imino compounds were obtained by interaction of α-aminoisobutyronitriles or 1-piperidinocyclohexanenitrile with phenyl- or *p*-chlorophenyllithium. Treatment of these imino compounds with a variety of acyl chlorides in benzene resulted in high yields of the acylimino derivatives shown in Table I. One of the imino compounds, 1-(1-benzimidoylcyclohexyl)piperidine, was a stable material; its melting point and infrared spectrum were unchanged after standing at room temperature for over 6 years.[2]

Of the variety of acyl derivatives of I (listed in Table I), the phenacetyl (**4**) and methylsulfonyl (**9**) analogs were the most active. The former compound was less active than phenmetrazine in mice and equipotent in the dog. All of the other compounds resulting from the above-mentioned structural changes were also less active than **4**.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrometer.

1-(2-Imino-1,1-dimethyl-2-phenylethyl)piperidine (Ia).—To a solution of 1 mole of phenyllithium in 700 ml of ether was added dropwise a solution of 75.0 g (0.46 mole) of α-piperidinoisobutyronitrile[3] in 200 ml of ether, and the mixture was refluxed for 2 hr. This solution was cooled and added to a solution of 110 g of NH_4Cl in 700 ml of water containing 200 g of ice. The layers were separated and the aqueous phase was extracted with ether. The organic layers were combined and dried ($MgSO_4$), and the solvent was evaporated. Fractionation of the residue gave 104 g (92%) of pale yellow distillate: bp 110–112° (0.2 mm); λ_{max}^{Nujol} 3.24 (NH), 6.19 μ (C=N).

Anal. Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 78.15; H, 9.67; N, 12.20.

Treatment of a solution of this material in ethanol with 1 equiv of alcoholic HCl and diluting the resulting solution with ether gave I (1).

Similarly, the interaction of α-dimethylaminoisobutyronitrile,[4] α-morpholinoisobutyronitrile (prepared by heating morpholine

(2) Several other stable imino compounds are known; see R. W. Layer, *Chem. Rev.*, **63**, 489 (1963).

(3) R. A. Jacobson, *J. Am. Chem. Soc.*, **67**, 1986 (1945).

(4) T. D. Perrine, *J. Org. Chem.*, **18**, 898 (1953).

and acetone cyanohydrin in the usual manner[3]), and 1-piperidinocyclohexanenitrile[5] with phenyllithium according to the above procedure gave the following compounds in 80–84% yield.

1-(2-Imino-1,1-dimethyl-2-phenylethyl)dimethylamine, bp 95–96° (2 mm). *Anal.* Calcd for $C_{12}H_{18}N_2$: N, 14.72. Found: N, 14.50.

1-(2-Imino-1,1-dimethyl-2-phenylethyl)morpholine, bp 115–120° (0.2 mm), mp 45–47° (hexane). *Anal.* Calcd for $C_{14}H_{20}N_2O$: N, 12.06. Found: N, 12.13.

1-(1-Benzimidoylcyclohexyl)piperidine, bp 148–151° (0.2 mm), mp 88–90° (hexane). *Anal.* Calcd for $C_{18}H_{26}N_2$: N, 10.36. Found: N, 10.24.

1-[2-Imino-1,1-dimethyl-2-(*p*-chlorophenyl)ethyl]piperidine.—A solution of 115 g (0.6 mole) of *p*-chlorobromobenzene in 600 ml of ether was stirred and cooled to −15° in an ice–salt bath and treated dropwise, over a period of 15 min, with 380 ml of 1.6 *N* *n*-butyllithium in hexane (0.6 mole) while maintaining the temperature at −7 to −12°. The pale yellow solution was stirred for an additional 30 min at −10° and then was treated with a solution of 76.0 g (0.5 mole) of α-piperidinoisobutyronitrile in 300 ml of ether. A yellow-orange precipitate began to separate from the mixture after about 30 min. After standing for 4 days at room temperature, the mixture was added to a cold NH_4Cl solution and processed in the manner described for Ia to give 96.2 g (73%) of pale yellow product, bp 155–158° (0.5 mm).

Anal. Calcd for $C_{15}H_{21}ClN_2$: N, 10.58. Found: N, 10.73.

1-(1,1-Dimethyl-2-phenacetylimino-2-phenylethyl)piperidine Hydrochloride (4).—A stirred solution of 40.0 g (0.17 mole) of Ia in 200 ml of benzene was maintained at 15–20° during the dropwise addition of a solution of 27.0 g (0.17 mole) of freshly distilled phenacetyl chloride in 100 ml of benzene. The mixture was refluxed for 1 hr, cooled, and filtered to give 62.5 g (93%) of product, mp 160–165°. After two crystallizations from 250-ml portions of isopropyl alcohol, the material weighed 39.3 g, mp 168–170°, λ_{max}^{Nujol} 5.85 and 5.98 μ (C=O and C=N).

1-(β-Amino-α,α-dimethylphenethyl)piperidine.—A solution of 29.9 g (0.13 mole) of Ia in 100 ml of ethanol was treated with 0.9 g of PtO_2. The mixture was placed in a Parr apparatus under 3 atm of hydrogen and heated to 50°. The theoretical quantity of hydrogen was consumed in 6 hr. The mixture was filtered and the filtrate was concentrated under reduced pressure to give 25.1 g (82%) of colorless product, bp 105–107° (0.1 mm), mp 56–59°. After crystallization from hexane, it melted at 61.5–63°.

Anal. Calcd for $C_{15}H_{24}N_2$: N, 12.06. Found: N, 11.83.

The HCl salt is **14** and the phenacetyl derivative is **15**.

The dimethylamino analog (above) was hydrogenated in a similar manner to give 64% yield of the amine, bp 87–89° (0.5 mm). The HCl salt is **16**.

2-Methyl-2-piperidinopropiophenone Hydrochloride (17).—To 170 ml of cold concentrated HCl was added 34.9 g (0.15 mole) of Ia; the mixture was refluxed for 24 hr, cooled, and treated with a solution of 100 g of NaOH in 130 ml of water. The product was extracted with ether and the combined ethereal solutions were dried ($MgSO_4$). After evaporation of the solvent, the residue was fractionated to give 31.8 g (91%) of pale yellow liquid, bp 100–101° (0.2 mm) [lit.[6] bp 110–112° (0.5 mm)]. This base was converted to the HCl salt in the usual manner (see preparation of Ia).

The ketones **19** and **20** were obtained in the same manner by hydrolysis of the corresponding imino compounds.

Appetite Depressant Test Procedure.—Mice were deprived of food (water *ad libitum*) for about 18 hr. Aqueous solutions of the test drugs were administered orally to groups of mice (10/dose) and after 15 min they were offered food pellets (Rockland Mouse Diet) for a period of 1 hr. The amount of food consumed during this period was then determined. The anorectic activity, expressed in milligrams per kilogram, is the approximate dose which caused a 50% decrease in the normal food intake. A similar test procedure was used when a compound was tested in dogs.

Acknowledgments.—The authors are indebted to A. Szabo, C. F. Turk, and J. Williams for the preparation of some of the compounds and to J. Alicino and his associates for the analyses reported herein.

(5) A. Katz and P. Merkel, *J. Prakt. Chem.*, **113**, 49 (1926).

(6) C. L. Stevens and C. H. Chang, *J. Org. Chem.*, **27**, 4392 (1962).

5-(3-Dimethylaminopropyl)-2,8-diaza-10,11-dihydro-5H-dibenzo[*b*,*f*]azepine

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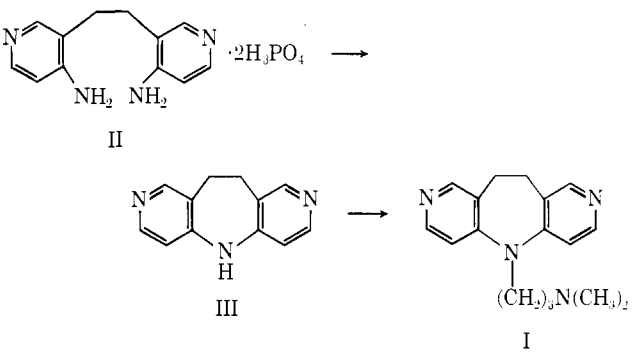
To study the biological effects of replacement of the aromatic rings by pyridine rings in the antidepressant drug, 5-(3-dimethylaminopropyl)-10,11-dihydro-5H-dibenzo[*b*,*f*]azepine,[1] the diaza compound I was prepared as shown in Chart I.

CHART I



Pyrolysis of 4,4′-diamino-3,3′-dipicolyl[2] as the diphosphate salt (II) at temperatures in the range of 300°[3] gave the tricyclic amine III, which was converted into I by alkylation with dimethylaminopropyl chloride and sodium hydride. The latter was characterized as the tetrahydrochloride and dimaleate salts.

The nmr spectrum of I,[4] measured in $CDCl_3$ with TMS as internal standard on the Varian A-60, is consistent with the assigned structure and shows: (a) the protons at positions 1 and 9 of the ring, being the least shielded are furthest downfield, show a singlet at δ 8.31 (2 H); (b) the doublets centered at δ 8.26 (2 H) and 6.95 (2 H) are assigned to the protons at positions 3,7 and 4,6 of the ring, respectively; (c) the bridge protons at C-10 and -11 appear as a singlet at δ 3.11 (4 H); (d) the triplets centered at δ 3.92 (2 H) and 2.30 (2 H) and the quintet at 1.77 (2 H) are the α, γ, and β protons, respectively, of the propyl side chain; (e) the strong singlet at δ 2.18 corresponds to the six protons of the $N(CH_3)_2$ group.

Compound I was remarkably inactive in most biological testing procedures. The compound at an oral dose of 10 mg/kg did not antagonize tetrabenazine-induced sedation[5] in mice. The standard[1] had an ED_{50} of 0.5 mg/kg in this test procedure. At oral doses of 2–15 mg/kg in the cat, no significant behavioral changes were noted. The ED_{50} *in vitro*

(1) Imipramine: W. Schindler and F. Häfliger, *Helv. Chim. Acta*, **37**, 472 (1954).

(2) E. C. Taylor, A. J. Crovetti, and N. E. Boyer, *J. Am. Chem. Soc.*, **79**, 3549 (1957).

(3) W. Schindler and F. Häfliger, U. S. Patent 2,764,580 (1956).

(4) The author is indebted to Mr. Milton D. Yudis of the Physical Organic Chemistry Department of the Schering Corp. for the interpretation of the nmr data.

(5) For a review of this procedure, see V. G. Vernier, H. M. Hanson, and C. A. Stone in "Psychosomatic Medicine," J. H. Nodine and J. H. Moyer, Ed., Lea and Febiger, Philadelphia, Pa., 1962, Chapter 80.