TABLE III

PHARMACOLOGICAL SCREENING RESULTS

Compd	Approx LD_{50}, mg/kg[a] Ip	Orat	Antidepressant act.[b] Dopa response potentiation test Ip	Orat
Ia	800	900	++	++
Ib	2000	>2000	+	+++
Id	2000	>2000	+	+
Ig	750	>1000	++	++
Ii	>2000	>2000	+	++
IIa	800	>1000	+	+
IIb	800	>1000	++	+
IIIa	150	850	+	+
IIIb	60	500	+	+
IIIc	125	750	+	++
IIId	125	750	+	++
IIIe	100	400	++	++
IIIf	150	750	++	++
IIIg	100	400	+++	++
IIIh	100	750	+	+
IIIi	150	850	+	+++
IIIj	500	1500	+	+
IIIk	125	750	+	+
IIIl	125	400	+++	++
IIIm	500	1000	+	++
IIIn	500	1000	+	++
IIIo	100	400	++	++
IVa	400	600	+	+
IVb	125	600	+	+
IVc	125	600	+	+
IVd	500	>1000	+	+
IVe	125	600	++	++
IVf	90	600	++	+
IVg	300	1000	+	++
VIa	60	500	++	+
VIb	40	200	+	+
VIc	60	400	+	++
VId	15	75		+++
Imipramine	150	400	+++	+++
Amitryptyline	80	350	+++	+++

[a] The dihydrochlorides were administered as 5% solutions in water and other insoluble compounds as 2% suspensions in 0.3% tragacanth to albino Swiss–Webster mice. [b] Reference 5. Dose, 25 mg/kg; activity at 4 hr.

7,8,9,10-Tetrahydro-6H-cyclohepta[*b*]quinoline-11-thione (IIa).—P_2S_5, 44.4 g (0.2 mole), was added to a stirred suspension of 42.6 g (0.2 mole) of 7,8,9,10-tetrahydro-6H-cyclohepta[*b*]-quinolin-11-one in 400 ml of pyridine. The mixture was refluxed for 3 hr and poured gradually into 1600 ml of hot water. After cooling to room temperature, the product was filtered and recrystallized.

Compounds IIb and IIc were prepared as above.

11-[3-(Dimethylamino)propoxy]-7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinoline (IIIc).—A mixture of 8.5 g (0.04 mole) of 7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinolin-11-one, 2.2 g (0.048 mole) of NaH (53.2% suspension in oil), and 250 ml of DMF was stirred and heated in an oil bath, maintained at 75–80° for 2 hr under N_2. 3-(Dimethylamino)propyl chloride (9.7 g, 0.08 mole) was added, dropwise, and the mixture was heated at 75–80° for an additional 3 hr. After cooling, the mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was diluted with H_2O and was extracted with ether. The extract was washed (H_2O), dried, and evaporated. The dihydrochloride was prepared by adding 2 equiv of HCl in *i*-PrOH to the residue (from ether extract) in EtOH, precipitated with ether, and refrigerated. All other compounds (III) were prepared as above except that IIIl and IIIn were isolated as bases.

11-[2-(Dimethylamino)ethylthio]-7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinoline (IVa).—A mixture of 5.7 g (0.025 mole) of 7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinoline-11-thione, 1.38 g (0.03 mole) of NaH (52% suspension in oil), and 80 ml of DMF was heated, with stirring, at 70–75° for 3 hr, under N_2. The solution was allowed to cool and 4.0 g (0.0375 mole) of 2-dimethylamino)ethyl chloride was added, dropwise. After the addition, the mixture was kept at 70–75° for 4 hr. On cooling, the mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was diluted with water and extracted with ether. The extract was washed (H_2O) and dried (Na_2SO_4). After removal of the solvent, the residue solidified and was recrystallized.

Compound IVd was prepared in the same manner; IVb e and IVe–g were isolated as dihydrochlorides.

2,11-Dichloro-7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinoline (Vb).—2-Chloro-7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinolin-11-one (58 g, 0.234 mole) was added under stirring to 80 ml of freshly distilled $POCl_3$, cooled in an ice bath. The mixture was allowed to warm up to room temperature and then refluxed for 1 hr. After cooling, the mixture was poured over 1 kg of crushed ice and stirred for a few minutes. After 1 hr at room temperature, $CHCl_3$ (250 ml) was added and the solution was basified with NH_4OH. The aqueous layer was separated and extracted twice ($CHCl_3$). The combined extract was washed (H_2O), dried, and evaporated *in vacuo*. The residue was recrystallized.

Compounds Va and Vc were obtained in the same manner.

11-[2-(Dimethylamino)ethylamino]-7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinoline (VIa).—A mixture of 11.5 g (0.05 mole) of 11-chloro-7,8,9,10-tetrahydro-6H-cyclohepta[*b*]quinoline,[1] 8.8 g (0.1 mole) of 2-(dimethylamino)ethylamine, 0.5 g of copper-bronze powder, and a few crystals of I_2 was heated in a closed steel cylinder at 180° for 24 hr, then treated with H_2O and ether. The aqueous layer was separated and extracted with ether. The combined ether solution was washed (H_2O) several times, dried, and evaporated *in vacuo*. The product was isolated as the dihydrochloride as in previous examples.

Compounds VIb–d were prepared in the same way.

Acknowledgments.—The author is grateful to Dr. N. Plotnikoff and his staff for the pharmacological test results and to Messrs. O. Kolsto and V. Rauschel and their staff for elemental analyses.

Hypocholesteremic Agents. IV. Some Substituted Piperazines

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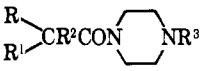
In a pharmacological study of chlorocyclizine[1a] and N-(β-phenyl-β-3-chlorophenyl-β-hydroxyethyl)-N′-methylpiperazine (**25**)[1b] Schmidt and Martin[2] found these compounds to be effective in causing a reduction in blood cholesterol concentration in mice although there was an increase in the cellular mass of the liver. This observation prompted us to prepare related compounds in the hope of finding one that would not show this adverse effect in the liver. This hope, however, was not realized. We prepared and tested 24 compounds related to the two piperazines mentioned above. These compounds showed varying degrees of lowering of blood cholesterol but this phenomenon was accompanied in general by an increased cellular mass in the liver. Many of the compounds had only weak activity and required the use of a high dosage. [*p*-

(1) (a) Diparalene®. (b) Prepared in this laboratory by R. J. Michaels and A. W. Weston.

(2) J. L. Schmidt and D. L. Martin, *Toxicol. Appl. Pharmacol.*, **7**, 257 (1965).

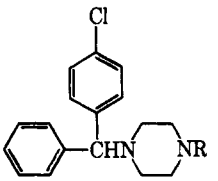
TABLE I



No.	R	R¹	R²	R³	Bp (mm) or mp, °C	Recrystn solvent or n_D (t, °C)[b]	Yield, %	Formula[a]
1	Xanthyl	...	H	Benzyl	169–168	Me–Ac	71	$C_{23}H_{24}N_2O_2$
2	Phenyl	Phenyl	H	Benzyl	124–126	Et_2O	93	$C_{25}H_{26}N_2O$
3	Phenyl	Allyl	H	Methyl	165 (2)	1.5406 (22.5)	54	$C_{16}H_{22}N_2O$[b]
4	Phenyl	*n*-Amyl	H	Methyl	174 (0.45)	1.5210 (22.5)	73.5	$C_{18}H_{28}N_2O$
5	*n*-Heptyl	*n*-Heptyl[d]	H	Methyl	172 (0.5)	1.4704 (23)	72	$C_{31}H_{42}N_2O$
6	Phenyl	Phenyl	OH	Benzyl	186–188	H_2O	74	$C_{25}H_{26}N_2O_2 \cdot HCl$
7	Phenyl	Phenyl	Cl	Benzyl	96–98	Et_2O	46	$C_{25}H_{25}ClN_2O$
9	Phenyl	Phenyl	Methoxy	Methyl	169–170	Et_2O	Low	$C_{20}H_{24}N_2O_2$
12	1-Naphthyl	...	...	Methyl	212 (1.6)		57	$C_{16}H_{18}N_2O$[c]
13	Phenyl	Phenyl	H	H[e]	208–210	MK–Sk	Low	$C_{20}H_{22}N_2O_2$
14	Phenyl	Phenyl	H	Methyl[f]	99–100	Et_2O	58	$C_{20}H_{24}N_2O \cdot H_2O$
15	Phenyl	Phenyl	H[g]		114–115	B	71	$C_{18}H_{19}NO$

[a] All compounds were analyzed for C, H. [b] C: calcd, 74.38; found, 75.02. [c] The hydrochloride had mp 280–285°. *Anal.* Calcd: C, 66.08; H, 6.59. Found: C, 65.78; H, 6.60. [d] We are indebted to Dr. Roger Adams for a supply of *n*-diheptylacetic acid. [e] A derivative of 2,2-dimethyl-3-ketopiperazine. [f] A derivative of homopiperazine. [g] A morpholinyl derivative. [h] Me–Ac = MeOH–Me_2CO, MK = butanone, Sk = Skellysolve B, B = benzene.

TABLE II



No.	R	Bp (mm) or mp, °C	Recrystn solvent[c]	Yield, %	Formula	Analyses
16	Cyanomethyl[a]		EA			
17	Aminoethyl[a]					
18	CH_2CONH_2 methylene carbamyl	156–158	DMF	66	$C_{19}H_{22}ClN_3O$	C, H
19	$COCH_3$	144–146	Et_2O	Low	$C_{19}H_{21}ClN_2O \cdot HCl$	N
20	$COCH_2Cl$	158–160	EtOH–Et_2O		$C_{19}H_{20}Cl_2 \cdot HCl$	C, H
21	COC_6H_5	126–128	Sk	72	$C_{24}H_{23}ClNO_2$	C, H
22	$CH_2COOC_2H_5$	222–230 (2)	T	50	$C_{21}H_{25}ClN_2O_2$	C, H
23	CH_3	110–112	Sk	71	$C_{18}H_{20}N_2O$[b]	C, H
24	$CH_2CH{=}CHC_6H_5$	111–112	Sk	54	$C_{26}H_{27}ClN_2$	C, H

[a] The preparation and physical constants of compounds **16** and **17** were reported by M. Freifelder, *J. Am. Chem. Soc.*, **82**, 2386 (1960). [b] Compound **23** contains the xanthyl radical. [c] EA = EtOH, DMF = dimethylformamide, T = toluene, Sk = Skellysolve B.

TABLE III. DECREASE OF BLOOD CHOLESTEROL

Compd	Calcd dose, mg/kg/day	Response, % redn	% increase in liver wt
1	400	31	..
	400	17	8
2	87.5	17	24
3	43.8	13	30
4	62.5	20	..
5	500	41	..
6	375	55	16
7	500	59	24
15	175	8	25
16	200	33	46
	200	38	33
17	62.5	53	2
	62.5	44	10
	31.2	20	18
18	62.5	21	..
	62.5	27	28
20	112.5	20	..
21	500	8	33
24	500	47	..
Triparanol	100	49	4
	10	27	..
Chlorocyclizine	40	33	51
25	26	44	19

(β-Diethylaminoethoxy)phenyl]-1-(*p*-tolyl)-2-(*p*-chlorophenyl)ethanol (triparanol), a known hypocholesteremic agent, was included in Table III as a control.

The compounds are reported in Tables I–III and were screened by a method previously described.[3]

Experimental Section[4]

Table I.—The compounds in this table were prepared by the acylation of a monosubstituted piperazine by the appropriate acid chloride in a conventional manner. They were purified by distillation or recrystallization from a suitable solvent.

Table II.—These compounds were prepared by the alkylation of a monosubstituted piperazine by a standard procedure. They were purified by distillation or recrystallization from a solvent.

Acknowledgment.—We are indebted to Orville Kolsto and the microanalytical staff for analytical data.

(3) H. B. Wright, D. A. Dunnigan, and U. Biermacher, *J. Med. Chem.*, **7**, 113 (1964).

(4) Melting points were taken on a calibrated Hoover capillary melting point apparatus. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values.