solved in methanol and decolorized with Norit. After filtration and concentration of the filtrate, 3.95 g. (33.4%) of the yellow crystalline acetate, m.p. 111–114°, was obtained. Repeated recrystallization from methanol produced an analytical sample in the form of yellow, blunt prisms, m.p. 120–120.5°; infrared absorption at 5.66, 5.95, and 8.32 μ; ultraviolet λ_{max} 325 mμ (log ϵ 4.22), shoulder 280 mμ (log ϵ 3.88).

Anal. Calcd. for $C_{18}H_{20}O_3S$: C, 68.30; H, 6.40. Found: C, 68.12; H, 6.22.

The yellow oil obtained from the filtrate, which remained after removal of the crystalline acetate, was evaporatively distilled between 120 and 140° (0.05 mm.). Nine fractions were collected which exhibited identical absorption in the infrared region, consistent with the acetoxy-α,β-unsaturated thiolactone structure; the combined fractions weighed 5.86 g. (49.5%); a center fraction was chosen for analysis.

Anal. Calcd. for $C_{18}H_{20}O_3S$: C, 68.30; H, 6.40. Found: C, 68.15; H, 6.28.

The **benzoate** of the phenolic thiolactone (IIc) was prepared by dissolving 200 mg. (0.634 mmole) of the crystalline acetoxyphenyl thiolactone (IId) in tetrahydrofuran, followed by the simultaneous addition of 11.64 ml. of 0.1089 *N* sodium hydroxide (1.27 mmole) and 0.089 g. (0.634 mmole) of benzoyl chloride. The mixture was allowed to shake overnight, followed by evaporation of the tetrahydrofuran. The product was taken up in ether, washed with water, and dried. Evaporation of the ether left a brown oil which was dissolved in benzene and decolorized with Norit. The benzoate crystallized from benzene–petroleum ether in the form of pale yellow prisms, m.p. 90–95°. Further recrystallization produced an analytical sample, m.p. 98–98.5°; infrared absorption at 5.77, 5.98, 7.95, and 8.32 μ; ultraviolet λ_{max} 232 mμ (log ϵ 4.33), 280 mμ (log ϵ 4.00), and 326 mμ (log ϵ 4.22).

Anal. Calcd. for $C_{23}H_{22}O_3S$: C, 72.99; H, 5.86. Found: C, 73.01; H, 5.79.

Acknowledgment.—We wish to express our appreciation to Drs. D. E. Clark, D. C. Burtner, and R. P. Ciula of this department for helpful discussions during the course of the work and to Dr. Roy Hertz for the physiological tests.

Hypocholesteremic Agents. I. Pyridyl Carbinols

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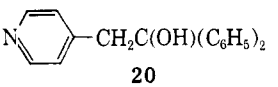
In a search for compounds showing tranquilizing properties, α,α-diphenyl-β-(4-pyridyl)ethanol (**20**) was



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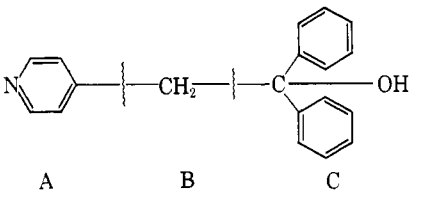
prepared by the action of benzophenone on 4-picolyl sodium.[1] This material when examined by our pharmacologists showed a marked activity in reducing serum cholesterol levels in the normal mouse. This observation stimulated our interest in the preparation and testing of other pyridyl carbinols. We were also interested in determining, if possible, what portions of the molecule were necessary for this observed diminution of the serum cholesterol content. The structure of the initial compound was divided into three portions with the



A B C

thought that a revamping of each portion would help to determine the site of activity. These variations were prepared by methods A and B in the Experimental.

Initially, we prepared and tested 1,1,2-triphenylethanol[2] and 1,2,2-triphenylethanol, two nonnitrogenous congeners. They showed little or no activity in our test and indicated the necessity for a basic ending in the molecule. Two compounds were prepared with a reduced hetero ring connected in the 1-position (**1**, **2**, Table I and II). Neither of these compounds had any activity. The substitution of 2-methylpyrazine for γ-picoline resulted in a product (**3**) that had no activity.

In our examination of the B portion of the molecule, branched chain condensation products were obtained by using 4-*n*-propylpyridine or 4-ethylpyridine, although the yields were poor. These products (**4**, **5**) showed some effectiveness at an intermediate dose, but at the lower dosage no activity was observed.

Other variations prepared involved the pyridyl grouping (α, β, or γ) adjacent to the hydroxyl and the phenyl substituent or the *p*-chloro derivative on the methylene carbon. None of these variations (**12**, **13**, **14**, **15**, **19**) conferred any cholesterol-lowering properties on the compounds except **15**. This material showed activity at a high dose level, but when the dosage was lowered, all activity disappeared.

When a substitution in portion C was made by 2-pyridyl, 3-pyridyl, methyl, and/or 4-pyridyl, the compound **16** was inactive, **8** was moderately active, while **17** and **18** showed activity only at a high dose level.

However, when one of the phenyl rings was replaced with a *p*-tolyl group, a very high dose of the compound (**6**) was active in the screening procedure. If the dosage was reduced, the activity disappeared.

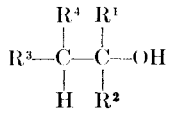
If the methyl group was substituted only in the pyridyl portion of the molecule, some activity was observed. When the methyl substituent was present in both of the phenyl rings and not in the pyridyl, the compound was again inactive. Finally, if a methyl group was introduced into the *para* position of one of the phenyl rings and another methyl group *ortho* in the pyridyl nucleus, activity was present when the compound was examined at a high and an intermediate dosage (see **11**, **10**).

Method of Screening.—The compounds were mixed intimately with ground mouse diet at the concentrations shown. By calculation using a typical mouse weight at 20 g. and the average daily food consumption per mouse 3 g. diet (found in previous experiments), the approximate daily dose in mg./kg./day can be determined. (For example a concentration of 0.067% in the diet equals approximately 100 mg./kg./day). The mice were housed in groups of six, weighed once as a group at the beginning of the experiment and once at the end. Control groups (usually at least 2) were given plain ground diet, and treated groups got ground diet containing drug. Access to diet and water was un-

(1) A. W. Weston and R. W. DeNet, personal communication.

(2) C. Hell and Fr. Weigandt, *Ber.*, **37**, 1429 (1904).

TABLE I



No.	R^1	R^2	R^3	R^4	B.p., °C. (mm.) or m.p., °C.	Recryst. solvent[a]	Method	% Yield	Formula	% Calcd. C	% Calcd. H	% Calcd. N	% Found C	% Found H	% Found N
20[b]	Phenyl	Phenyl	1-Pyridyl	H	159–160	EtOH	A	61	$C_{19}H_{17}NO$	82.88	6.22	5.08	83.10	6.12	5.08
1	Phenyl	4-Chlorobenzyl	1-Piperidyl	H	82–84	MeOH	B	Low	$C_{20}H_{24}ClNO$	72.82	7.33		72.97	6.75[e]	
2[d]	Phenyl	Phenyl	1-Piperidyl	H	195–200 (2.8)		B	25	$C_{19}H_{23}NO$	81.10	8.24		80.94	8.19	
3	Phenyl	Phenyl	2-Pyrazinyl	H	153–154	EtOH–H_2O	A	22	$C_{18}H_{16}N_2O$	78.23	5.84		78.50	5.86	
4	Phenyl	Phenyl	4-Pyridyl	$-CH_2CH_3$	136–137	Et–Sk	A	8	$C_{21}H_{21}NO$	83.13	6.98		83.15	6.87	
5	Phenyl	Phenyl	4-Pyridyl	$-CH_3$	137–138	Acetone–H_2O	A	7	$C_{20}H_{19}NO$	83.02	6.61		82.76	6.65	
6	*p*-Tolyl	Phenyl	4-Pyridyl	H	154–156	EtOH–H_2O	A	68	$C_{20}H_{19}NO$	83.02	6.61		83.23	6.68	
7	*p*-Tolyl	*p*-Tolyl	4-Pyridyl	H	171	EtOH–H_2O	A	42	$C_{21}H_{21}NO$	83.13	6.98		83.11	7.18	
8	Methyl	4-Pyridyl	4-Pyridyl	H	Crude[c]		A	35	$C_{13}H_{14}N_2O$[f]	72.88	6.58		72.85	6.86	
9	Methyl	2-Pyridyl	4-Pyridyl	H	152–153 (0.6) 56–58		A	34	$C_{13}H_{14}N_2O$	72.88	6.58	13.08	72.53	6.70	12.96
10	*p*-Tolyl	Phenyl	3-Methyl-4-pyridyl	H	171–172	*i*-Pr	A	59.5	$C_{21}H_{21}NO$	83.15	6.96	4.61	82.58[e]	6.93	4.66
11	Phenyl	Phenyl	2-Methyl-4-pyridyl	H	201–202	*i*-Pr	A	84.8	$C_{20}H_{19}NO$	83.02	6.61	4.84	82.78	6.91	4.92
12	Phenyl	4-Pyridyl	4-Chlorophenyl	H	177–178	Bz	B	8.9	$C_{19}H_{16}ClNO$	73.65	5.20		73.60	5.44	
13	Phenyl	2-Pyridyl	4-Chlorophenyl	H	145–147	Bz	B	9.4	$C_{19}H_{16}ClNO$	73.65	5.20		72.97	5.47	
14	Methyl	6-Methyl-3-pyridyl	4-Chlorophenyl	H	177–180 (0.8)		B	65.7	$C_{15}H_{16}ClNO$	68.82	6.16		68.63	6.32	
15	Methyl	4-Pyridyl	4-Chlorophenyl	H	146–148	Acetone	B	26.3	$C_{14}H_{13}ClNO$	67.87	5.69		68.23	5.77	
16[g]	Phenyl	4-Pyridyl	4-Pyridyl	H	194–196	Acetone	A	19.5	$C_{18}H_{16}N_2O$	78.23	5.83		78.07	5.76	
17	Phenyl	3-Pyridyl	4-Pyridyl	H	110	Acetone–pentane	A	38.7	$C_{18}H_{16}N_2O \cdot H_2O$	73.45	6.16		73.42	6.31	
18	Phenyl	2-Pyridyl	4-Pyridyl	H	120–121	BzSk	A	50.6	$C_{18}H_{16}N_2O$	78.23	5.83		78.63	5.71	
19	Methyl	3-Pyridyl	4-Chlorophenyl	H	176–181 (0.8–1.0)[h] 84–86		B	22.6	$C_{14}H_{13}ClNO$	67.87	5.69		68.10	5.89	

[a] MeOH = methyl alcohol, EtOH = ethyl alcohol, Et = ethyl ether, Sk = Skellysolve B, Bz = benzene, *i*-Pr = isopropyl alcohol. [b] This compound was reported by C. H. Tilford and M. G. Van Campen, Jr., *J. Am. Chem. Soc.*, **76,** 2431 (1954), but with a melting range 122–124°. [c] The average of two analyses. [d] A. L. Morrison, R. F. Long, and M. Königstein, *J. Chem. Soc.*, 952 (1951), reported this compound to have a melting point 65–66° and characterized it by nitrogen analysis. E. Lindner and L. Stein, *Arzneimittel Forsch.*, **9,** 94 (1959), listed this compound in a table as a hydrochloride but do not report the base or list any physical constants. [e] Decomposes on distillation. [f] The oxygen analysis calcd., 7.46; found 7.89. [g] After we prepared this compound, it became available from Reilly Tar and Chemical Corp. [h] This compound was reported by M. Pesson and M. Antoine, *Compt. Rend.*, **256,** 193 (1963), to have m.p. 90°. On repeated recrystallization of our sample, some decomposition was observed.

TABLE II

Compound	Calculated dose, mg./kg./day	Concentration, % in diet	Response,[a] % reduction
20	400	0.267	36
	100	.067	38
	40	.027	36
	20	.013	36
	10	.007	29
	5	.0033	11
	2.5	.0017	4
1	312	.208	6
2	156	.104	4
4	100	.067	27
	10	.007	0
5	100	.067	36
6	500	.333	48
8	250	.167	31
10	500	.333	65
	100	.067	22
11	100	.067	30
15	312	.208	34
	100	.067	0
16	75	.050	6
17	219	.146	57
	10	.007	0
18	100	.067	46
	10	.007	5
22	500	.333	9
	250	.167	17
	100	.067	49
Triparanol	100	.067	49
	10	.007	27

[a] $\%\ \text{reduction} = 100\left(1 - \frac{\text{mg.\% cholesterol treated}}{\text{mg.\% cholesterol control average}}\right)$

limited. At the end of treatment (1 or 2 weeks) the mice were bled by heart puncture, the bloods were centrifuged, and the plasma separated. Cholesterol determination was done on the plasma for each mouse.

Experimental[3]

Preparation of Carbinols. Sodamide (Method A).—Sodamide was added portionwise to an excess of γ-picoline stirred and cooled in ice–water. This mixture frequently became very dark as the picolyl sodium formed. The appropriate ketone dissolved in additional γ-picoline was added very rapidly and the resulting mixture was stirred overnight. This mixture was then poured into a large excess of water and allowed to crystallize. After filtering, the products could then be recrystallized from a suitable solvent.

General Grignard Procedure (Method B).—To the Grignard solution prepared from 0.2 g.-atom of magnesium and 0.2 mole of *p*-chlorobenzyl chloride in 100 ml. of ether was slowly added a suspension of 0.19 mole of the pyridyl ketone in 300 ml. of ether with stirring. The mixture was then heated to reflux for 4 hr. with continued stirring. The reaction mixture was then decomposed by the addition of an equivalent of ammonium chloride in saturated aqueous solution. The salts were filtered and washed with more ether which was then concentrated to an oil by distilling the ether. The residual oil was distilled *in vacuo* and the product recrystallized from a suitable solvent.

Acknowledgment.—We are indebted to Dr. John Schmidt and Don Martin for the pharmacological screening and to E. F. Shelberg and his staff for analytical data. We wish to thank Dr. James Short of the Organic Chemistry Department for help and suggestions.

(3) Melting points were taken on a Hoover capillary melting point apparatus with the thermometer calibrated against melting point standards.

Hexahydropyrimidines. IV.[1] Synthesis of 2-[4-(N,N-Bis(2-chloroethyl)amino)aryl]-1,3-bis-(aralkyl)hexahydropyrimidines as Antitumor Agents[2]

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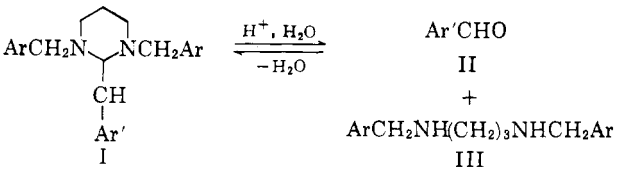
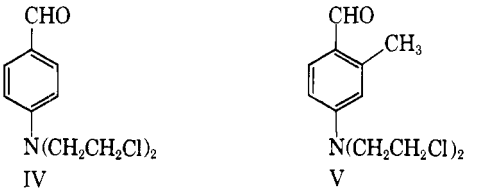
In a recent publication, the synthesis of a number of 1,2,3,-substituted hexahydropyrimidines as potential antitumor agents was reported.[1] It was suggested that these compounds I may be thought of as potential aldehydes, since they can hydrolyze under mild acid conditions to liberate the free aldehyde II.



The available test data for those hexahydropyrimidines indicated no significant activity when screened in the carcinoma 755, sarcoma 180, and leukemia 1210 systems. However, the 2-substituted 1,3-bis(*p*-methoxybenzyl)hexahydropyrimidines prepared from benzaldehyde, 2,4-dichlorobenzaldehyde, and *o*-ethoxybenzaldehyde displayed reproducible activity in a tissue culture screen. These results suggest that possibly a more potent cytotoxic aldehyde is necessary for *in vivo* antitumor activity. To this end, hexahydropyrimidines have been prepared from benzaldehyde nitrogen mustard IV and *o*-tolualdehyde nitrogen mustard V.



Due to the potential alkylating action of the nitrogen mustard grouping, the derivatives of these aldehydes might show selective antitumor activity if they are released preferentially at the tumor site, unless, of course, the nitrogen mustard grouping is capable of more rapid alkylation from the hexahydropyrimidine transport molecule.

The hexahydropyrimidines reported in Table I were synthesized by condensing the aldehydes IV or V with secondary 1,3-diamines of the general structure III in a refluxing solution of ethanol or acetonitrile. The latter solvent was found to be much preferred in two of the syntheses. The diamines III were prepared by reduction of the corresponding di-Schiff base VI.

(1) J. H. Billman and J. L. Meisenheimer, part III: *J. Med. Chem.*, **6**, 682 (1963).

(2) This investigation was supported by a Public Health Service Fellowship (GF-13,650) from the Division of General Medical Sciences, National Institutes of Health, Public Health Service.

(3) National Institutes of Health Fellow, 1961–1963. Taken from the Ph.D. thesis of J. L. M., Indiana University, 1963.