tion was freed of solvent by distillation through a short column, yielding an olefin residue weighing 0.73 g. (106 %), having $n^{23}D$ 1.5277, showing infrared olefinic bands at 11.23, 12.45 and 12.90 μ, and showing no infrared hydroxyl absorption. The alumina column was then eluted with one liter of absolute ethanol. The eluate was freed of solvent through a column, and the residue was subjected to rotary evaporation at aspirator pressure, yielding 1.79 g. of residual oil, $n^{22}D$ 1.4890. The infrared spectrum of this oil showed no absorption at 11.23 or 12.90 μ, but a strong OH band at 2.95 μ. A sample of this oil was subjected to VLPC on packing B (pressure of helium, approx. 2 p.s.i.). Two peaks at 14.5 and 40.2 minutes were observed. Since the 2-phenyl-2-butanol (VI) component in the original reaction mixture had been shown previously to dehydrate quantitatively to an olefin, the two presently observed peaks in the VLP chromatogram corresponded, respectively, to 1-phenyl-2-methyl-1-propanol (14.5 min.) and 3-phenyl-2-butanol (40.2 min.). The efflux time differences between this and the previous VLP chromatogram were due to differences in the helium carrier gas pressure.

The above deamination mixture (1.57 g.) was dissolved in anhydrous acetic acid (100 ml.), and the solution was maintained at 75° for 26 hours. Similar alumina column chromatography led to an olefin fraction weighing 0.23 g., and showing an identical infrared pattern as the olefin from the above synthetic mixture. Further elution of the alumina column with ethanol, as above, led to a carbinol residue of 1.27 g., having an infrared spectrum identical with that of the previous synthetic mixture at the same stage. A VLP chromatogram was run (packing B, *ca.* 2 p.s.i. helium pressure) on this carbinol residue, resulting in peaks at 14.5 and 40.2 minutes, corresponding to 1-phenyl-2-methyl-1-propanol and 3-phenyl-2-butanol, respectively. The planimeter determined area under the 14.5 min. peak was 1.04 in.², and that under the 40.2 min. peak was 4.23 in.². These data, involving the weight of the olefin fraction and the areas under the peaks of the other two carbinol fractions, permit the calculation that the composition of the crude deamination mixture was approximately 67% 3-phenyl-2-butanol (V), 16.5% 2-phenyl-2-butanol (VI) and 16.5% 1-phenyl-2-methyl-1-propanol (VII). The discrepancy (50% *vs.* 67%) in the quantity of 3-phenyl-2-butanol between this and the above estimation, is presumably within the experimental error of the rather coarse analytical methods employed.

STANFORD, CALIFORNIA

[CONTRIBUTION FROM THE MILES-AMES RESEARCH LABORATORY]

Some New Amebicidal Diamines[1]

BY OTIS E. FANCHER, SHIN HAYAO AND GUST NICHOLS

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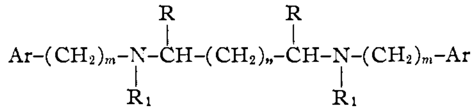
A number of bis-aminoalkanes and the related bis-tetrahydro-1-isoquinolylalkanes have been prepared for testing as amebicidal and trypanocidal agents. Some of these compounds showed sufficient activity *in vitro* to warrant *in vivo* and clinical study.

Emetine has been much used as a prototype for the synthesis of new compounds in the search for a more effective amebicide. Both open-chain bis-amines[2] and bis-tetrahydroisoquinolines[3] have been studied for this purpose and several have been reported to be effective both *in vitro* and *in vivo*. Of the open chain bis-amines, those of Hall, *et al.*,[2b] were of particular interest. They reported 7,13-diamino-5,15-diethylnonadecane dihydrochloride to be active *in vitro* against *E. histolytica* at a dilution of 1:500,000.

Thinking that reductive alkylation of amines of this type with alkoxy aromatic aldehydes would give compounds having a closer formal relationship to emetine, we have prepared a series represented by the general formula



$$\mathrm{Ar{-}(CH_2)_m{-}\underset{R_1}{N}{-}\overset{R}{C}H{-}(CH_2)_n{-}\overset{R}{C}H{-}\underset{R_1}{N}{-}(CH_2)_m{-}Ar}$$

$R = H, C_2H_5, n\text{-}C_4H_9, i\text{-}C_5H_{11}$ and C_6H_{11}
$R_1 = H$ or CH_3
$m = 1$ or 3; $n = 0, 2, 4, 5, 6$ and 10
$Ar = C_6H_5, 4\text{-}(HO)C_6H_4, 4\text{-}(MeO)C_6H_4, 3,4\text{-}(CH_2O_2)C_6H_3, 3,4\text{-}(MeO)_2C_6H_3, 3,4\text{-}(MeO)_2C_6H_3$ and $3,4,5\text{-}(MeO)_3C_6H_2$

The primary amines required for this study were prepared by the method of Hall,[2b] which involves a Schmidt reaction on a dicarboxylic acid prepared by a malonic ester synthesis. When R is not hydrogen the dicarboxylic acids, the diamines, the Schiff bases and the final products are capable of existing as racemic and *meso* forms. In the only member of the series which was studied extensively, ($R = n\text{-}C_4H_9$, $n = 5$, $m = 1$ and $Ar = 3,4\text{-}(CH_2O_2)C_6H_3$), the intermediate dicarboxylic acid was obtained as a heavy oil from which a crystalline product could be isolated by crystallization from ligroin (b.p. 60–90°). The non-crystalline residue from evaporation of the solvent could be partially isomerized by distillation followed by crystallization of the distillate from ligroin (b.p. 60–90°), and this process could be repeated several times to give additional quantities of the crystalline acid. The presumed unstable isomer was not isolated and the stereochemical structure of the crystalline acid was not determined.

That the crystalline acid was not stereochemically pure was suggested by the isolation of two Schiff bases on reaction of the derived diamine with piperonal. The major portion of the Schiff base melted at 105–107° and on reduction gave a final product melting at 180–182°. When working with large quantities of material a small amount of Schiff base melting at 74–74.5° was isolated by fractional crystallization from absolute alcohol.

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[1] Presented at the 132nd National Meeting of the American Chemical Society, September 10, 1957, New York, N. Y. (Abstracts p. 21-O).

[2] (a) F. L. Pyman, *J. Soc. Chem. Ind.*, **56**, 789 (1937); (b) D. M. Hall, S. Mahboob and E. E. Turner, *J. Chem. Soc.*, 149 (1952); (c) J. A. Goodson, *et al.*, *Brit. J. Pharmacol.*, **3**, 49 (1948).

[3] (a) R. Child and F. L. Pyman, *J. Chem. Soc.*, 2010 (1929); (b) G. Hahn, *Ber.*, **71B**, 2183, 2187 (1938); (c) C. M. Smith, *et al.*, *J. Pharmacol. Exptl. Therap.*, **108**, 317 (1953); (d) P. N. Craig and F. P. Nabenhaver, U. S. Patent 2,659,728 (1953); *cf. C. A.*, **48**, 12182 (1954); (e) M. Onda, Japanese Patent 8030 (1954); (f) A. Dobrowsky, *Monatsh.*, **86**, 27 (1955).

This on reduction gave a final product melting at 175–176°, mixed m.p. 163–165°. Since the Schmidt reaction occurs with retention of configuration[4] it seemed likely that the crystalline dicarboxylic acid was not a single substance.

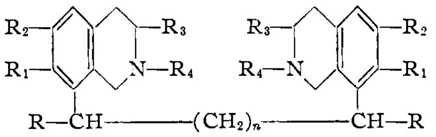
The compounds of the generic formula where $m = 1$ were prepared by reaction of the primary amines with the appropriate aldehyde followed by reduction using Adams platinum oxide catalyst[5] at three atmospheres pressure at room temperature in absolute alcohol when the intermediate Schiff base was soluble. For relatively insoluble Schiff bases reduction was accomplished at 50–75 atmospheres at 80° using a Raney nickel catalyst[6] in absolute alcohol. In only a few cases were the Schiff bases isolated and characterized.

Where $m = 3$, the compounds were prepared by reductive alkylation with the appropriate cinnamaldehyde or by lithium aluminum hydride reduction in tetrahydrofuran of the diamides formed from the reaction of the primary diamines with the appropriate hydrocinnamic acid.

The phenolic compounds were derived from the corresponding methoxy derivatives by demethylation with 48% hydrobromic acid in glacial acetic acid and the tertiary amines were made by methylation of the secondary amines with formaldehyde and formic acid.[7]

The phenolic compounds were characterized as dihydrobromides and all other compounds as dihydrochlorides. The compounds prepared are given in Table I.

The investigation was extended to include some bis-tetrahydroisoquinolines having the general structure



$R = H, C_2H_5, n\text{-}C_4H_9$ and $i\text{-}C_5H_{11}$
$R_1 = R_2 = CH_3O$ or $R_1 + R_2 = CH_2O_2$
$R_3 = H$ or CH_3; $R_4 = H$ or CH_3

These products were conveniently prepared from the diamides made from the dicarboxylic acids and the appropriate phenethylamine either directly by heating or via the acid chlorides using the Bischler–Napieralski reaction[8] followed by reduction of the intermediate bis-dihydroisoquinolines using a platinum oxide catalyst. N-Methylation was accomplished either by treating the tetrahydroisoquinoline with formalin and formic acid or by hydrogenation of the bis-dihydroisoquinoline dimethiodide.[3a] The latter was the more satisfactory method. No extensive effort was made to separate the possible isomers in pure form.

The amides prepared are given in Table II, the characterized bis-dihydroisoquinolines are shown in Table III and the bis-tetrahydroisoquinolines are summarized in Table IV.

Biological Activity.[9]—Toxicities of the compounds were determined by intraperitoneal administration to mice and orally in the rat. The *in vitro* amebicidal activities were determined by the W.E.L. method using *E. histolytica* supported by organism "t," tests being made at 1000, 100, 50 and 10 γ/ml. By this test emetine is amebicidal at 10 γ/ml. *In vitro* trypanocidal activity was determined using *T. cruzi*.[10] Many of the compounds of both series were found to be amebicidal at 50 γ/ml. and many were also trypanocidal *in vitro*. *In vivo* activity in the monkey[11] has been demonstrated for several compounds and effectivness in clinical amebiasis[12] has been shown for N,N'-dipiperonyl-5,11-diaminopentadecane dihydrochloride. None of the compounds showed activity against *T. cruzi* or *T. gambiense in vivo*.[13] The compounds are very much less toxic than emetine. Further clinical evaluation is in progress.

Conversion to tertiary amines or to phenols decreases amebicidal activity. Branching of the chain connecting the amine functions appears to be important for appreciable activity since no compound with an unbranched chain showed an interesting degree of activity. There is a trend toward increased activity in a particular series as the size of the branching alkyl substituent is increased from ethyl to butyl or isoamyl. This factor is being studied further. Increased chain length decreases the toxicity and increases the difference between intraperitoneal and oral toxicity, very probably because of changes in solubility. Variations in the aromatic substituent produce no consistent change in activity, but such substituents contribute to activity since the primary amines showed no interesting degree of activity by the test methods used.

Experimental[14]

Tetraethyl 5,5,11,11-Pentadecanetetracarboxylate.—Sodium (131 g. 5.7 moles) in four liters of xylene was heated to reflux and 1233 g. (5.67 moles) of diethyl *n*-butylmalonate was added dropwise, keeping the temperature above the melting point of sodium. The mixture was refluxed for an hour after addition was complete. There was added 655 g. (2.85 moles) of 1,5-dibromopentane and the mixture was refluxed for four hours. After cooling, two liters of water was added and the organic layer was separated. The aqueous layer was extracted with ether and the combined ether and xylene solutions were washed with water and dried over magnesium sulfate. The solvents were removed by distillation and the fraction distilling up to 196° at 0.5 mm. (235 g.) was removed. The residual ester weighed 955 g. This could be distilled with some loss by decomposition at 208–212° (0.6 mm.).

5,11-Pentadecanedicarboxylic Acid.—The crude tetracarboxylic acid ester, 955 g., was dissolved in 2400 ml. of 95%

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[4] M. S. Newman and H. L. Gildenhorn, THIS JOURNAL, **70**, 317 (1948).

[5] Baker and Co., Inc., Newark, N. J.

[6] Raney active nickel catalyst in water from Raney Catalyst Co., Chattanooga, Tenn. This was washed free of alkali and dried by washing with absolute alcohol.

[7] A. R. Surrey, *et al.*, THIS JOURNAL, **71**, 2421 (1949).

[8] W. M. Whaley and T. R. Govindachari, "Organic Reactions," Vol. VI, John Wiley and Sons, New York, 1951, p. 74.

[9] We are indebted to Dr. R. K. S. Lim of the Pharmacology Section and to Dr. L. B. Schweiger and Mr. Wm. A. Beppler of the Microbiology Section of this Laboratory for these tests.

[10] Wm. A. Beppler and L. B. Schweiger, *Antibiotics & Chemotherapy*, **7**, 513 (1957).

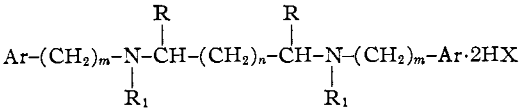
[11] A. K. Hrenoff and H. H. Anderson, *Federation Proc.*, **15**, 721 (1956).

[12] H. H. Anderson, *et al.*, paper presented at the Annual Meeting of the American Society of Tropical Medicine and Hygiene, November 3, 1956.

[13] A. Packchanian, private communication.

[14] Melting points are corrected. Ultraviolet spectra were determined in methanol using a Warren Spectracord.

TABLE I



$$\mathrm{Ar{-}(CH_2)_{\mathit{m}}{-}\underset{R_1}{\underset{|}{N}}{-}\overset{R}{\overset{|}{C}}H{-}(CH_2)_{\mathit{n}}{-}\overset{R}{\overset{|}{C}}H{-}\underset{R_1}{\underset{|}{N}}{-}(CH_2)_{\mathit{m}}{-}Ar\cdot 2HX}$$

Ar	*m*	R	R₁	*n*	X	Formula	M.p., °C.	Method[a]	Yield, %	Nitrogen, %	
										Calcd.	Found
4-$(CH_3O)C_6H_4$	1	H	H	0	Cl	$C_{18}H_{26}Cl_2N_2O_2$	285–287	B	90	7.51	7.60
3,4-$(CH_2O_2)C_6H_3$	1	C_2H_5	H	4	Cl	$C_{26}H_{38}Cl_2N_2O_4$	252–253	A	85	5.46	5.32
3,4-$(CH_2O_2)C_6H_3$	1	C_2H_5	CH_3	4	Cl	$C_{28}H_{42}Cl_2N_2O_4$	235–237	C	63	5.17	5.09
3,4-$(CH_2O_2)C_6H_3$	1	*n*-C_4H_9	H	4	Cl	$C_{30}H_{46}Cl_2N_2O_4$	193–195	A	73	4.92	4.87
4-$(HO)C_6H_4$	1	*i*-C_5H_{11}	H	4	Br	$C_{30}H_{50}Br_2N_2O_2$	97–98	D	67	4.44	4.43
4-$(CH_3O)C_6H_4$	1	*i*-C_5H_{11}	H	4	Cl	$C_{32}H_{54}Cl_2N_2O_2$	53–54	B	76	4.92	4.79
3,4-$(CH_2O_2)C_6H_3$	1	*i*-C_5H_{11}	H	4	Cl	$C_{32}H_{50}Cl_2N_2O_4$	86–88	A	82	4.69	4.82
C_6H_5	1	C_6H_{11}	H	4	Cl	$C_{32}H_{50}Cl_2N_2$	259–264	B	91	5.26	5.30
4-$(HO)C_6H_5$	1	C_6H_{11}	H	4	Br	$C_{32}H_{52}Br_2N_2O_2$	Glass	D	62	4.28	4.25
4-$(CH_3O)C_6H_4$	1	C_6H_{11}	H	4	Cl	$C_{34}H_{54}Cl_2N_2O_2$	257–258	B	91	4.72	4.79
3,4-$(CH_2O_2)C_6H_3$	1	C_6H_{11}	H	4	Cl	$C_{34}H_{50}Cl_2N_2O_4$	230–232	B	89	4.51	4.50
3,4-$(CH_3O)_2C_6H_3$	1	C_6H_{11}	H	4	Cl	$C_{36}H_{58}Cl_2N_2O_4$	237–245	B	86	4.28	4.32
3,4,5-$(CH_3O)_3C_6H_2$	1	C_6H_{11}	H	4	Cl	$C_{38}H_{62}Cl_2N_2O_4$	236–239	B	84	3.93	3.86
3,4-$(CH_2O_2)C_6H_3$	1	*n*-C_4H_9	H	5	Cl	$C_{31}H_{48}Cl_2N_2O_4$	180–182	B	93	4.80	4.78
							175–176[b]	B	91	4.80	4.75
3,4-$(CH_3O)_2C_6H_3$	1	*n*-C_4H_9	H	5	Cl	$C_{33}H_{56}Cl_2N_2O_4$	126–128	A	87	4.54	4.62
3,4-$(CH_2O_2)C_6H_3$	1	*n*-C_4H_9	CH_3	5	Cl	$C_{33}H_{52}Cl_2N_2O_4$	142–144	C	67	4.58	4.32
3,4-$(CH_2O_2)C_6H_3$	1	*i*-C_5H_{11}	H	5	Cl	$C_{33}H_{52}Cl_2N_2O_4$	74–76	A	78	4.58	4.71
3,4-$(CH_3O)_2C_6H_3$	1	*i*-C_5H_{11}	H	5	Cl	$C_{35}H_{60}Cl_2N_2O_4$	67–69	A	81	4.36	4.55
C_6H_5	3	*i*-C_5H_{11}	H	5	Cl	$C_{35}H_{60}Cl_2N_2$	Glass	E	64	4.83	4.87
4-$(CH_3O)C_6H_4$	3	*i*-C_5H_{11}	H	5	Cl	$C_{37}H_{64}Cl_2N_2O_2$	233–236	E	76	4.38	4.34
3,4-$(CH_2O_2)C_6H_3$	1	C_2H_5	H	6	Cl	$C_{28}H_{42}Cl_2N_2O_4$	254–256	A	87	5.17	5.09
3,4-$(CH_2O_2)C_6H_3$	1	C_2H_5	CH_3	6	Cl	$C_{30}H_{46}Cl_2N_2O_4$	215–217	C	67	4.93	4.87
3,4-$(CH_3O)_2C_6H_3$	1	C_2H_5	H	6	Cl	$C_{30}H_{50}Cl_2N_2O_4$	212–215	A	91	4.88	4.78
C_6H_5	1	*n*-C_4H_9	H	6	Cl	$C_{30}H_{50}Cl_2N_2$	186–188	B	59	5.50	5.55
4-$(HO)C_6H_4$	1	*n*-C_4H_9	H	6	Br	$C_{30}H_{50}Br_2N_2O_2$	180–182	D	71	4.44	4.42
4-$(CH_3O)C_6H_4$	1	*n*-C_4H_9	H	6	Cl	$C_{32}H_{54}Cl_2N_2O_2$	160–164	A	93	4.96	4.96
3,4-$(CH_2O_2)C_6H_4$	1	*n*-C_4H_9	H	6	Cl	$C_{32}H_{50}Cl_2N_2O_4$	186–189	A	89	4.68	4.72
3,4-$(CH_3O)_2C_6H_4$	1	*n*-C_4H_9	H	6	Cl	$C_{34}H_{58}Cl_2N_2O_4$	163–166	A	90	4.45	4.47
3,4,5-$(CH_3O)_3C_6H_2$	1	*n*-C_4H_9	H	6	Cl	$C_{36}H_{62}Cl_2N_2O_4$	130–134	A	81	4.07	4.00
4-$(CH_3O)C_6H_4$	3	H	H	6	Cl	$C_{26}H_{42}Cl_2N_2O_2$	298–302	F	76	5.77	5.83
3,4-$(CH_3O)_2C_6H_3$	3	H	H	6	Cl	$C_{28}H_{46}Cl_2N_2O_2$	199–205	F	42	5.14	5.17
3,4-$(CH_2O_2)C_6H_3$	1	H	H	7	Cl	$C_{23}H_{32}Cl_2N_2O_4$	280–281	B	94	5.82	5.89
C_6H_5	1	C_2H_5	H	10	Cl	$C_{30}H_{50}Cl_2N_2$	Glass	B	62	5.51	5.66
4-$(HO)C_6H_4$	1	C_2H_5	H	10	Br	$C_{30}H_{50}Br_2N_2O_2$	Glass	D	57	4.44	4.35
3,4-$(CH_2O_2)C_6H_3$	1	C_2H_5	H	10	Cl	$C_{32}H_{50}Cl_2N_2O_4$	Glass	B	71	4.70	4.91
3,4-$(CH_3O)_2C_6H_3$	1	C_2H_5	H	10	Cl	$C_{34}H_{58}Cl_2N_2O_4$	156–158	B	82	4.46	4.50
3,4,5-$(CH_3O)_3C_6H_2$	1	C_2H_5	H	10	Cl	$C_{36}H_{62}Cl_2N_2O_4$	Glass	B	66	4.07	4.09
4-$(CH_3O)C_6H_4$	1	*n*-C_4H_9	H	10	Cl	$C_{36}H_{63}Cl_2N_2O_2$	Glass	B	59	4.47	4.57
3,4-$(CH_2O_2)C_6H_3$	1	*n*-C_4H_9	H	10	Cl	$C_{36}H_{58}Cl_2N_2O_4$	Glass	B	61	4.29	4.34
3,4-$(CH_3O)_2C_6H_3$	1	*n*-C_4H_9	H	10	Cl	$C_{38}H_{66}Cl_2N_2O_4$	Glass	B	52	4.08	4.04

[a] A, low pressure with Adams catalyst. B, high pressure with Raney nickel; C, formic acid–formaldehyde methylation D, demethylation with 48% HBr–HOAc; E, reductive alkylation with the appropriate cinnamaldehyde using Ni (R); F, $LiAlH_4$ reduction of the hydrocinnamamide in THF. [b] Low melting isomer.

ethanol, treated with 850 g. of potassium hydroxide dissolved in 1200 ml. of water and the solution was refluxed for 96 hours. An additional two liters of water was added and ethanol was removed by distillation. The aqueous residue was carboned and acidified with concentrated hydrochloric acid. The crude acid was filtered, washed with water and dried.

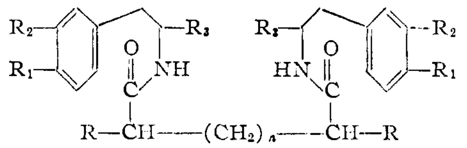
The crude acid, 765 g., was decarboxylated by heating in an oil-bath at 175–185° for three hours in an open flask. The crude product, 590 g., was dissolved in hot ligroin (b.p. 90–120°), carboned, filtered and chilled. The crystalline product which separated weighed 202 g. and melted at 88–90°. Distillation of the residue gave 240 g. of product boiling at 219–220° (0.5 mm.). This solidified on cooling and crystallization as above gave 129 g. of crystalline product which melted at 87–90°. An additional 56 g. of crystalline acid was obtained by another distillation and recrystallization of the residue. The total yield of crystalline acid was 387 g. or 45.3%.

Anal. Calcd. for $C_{17}H_{32}O_4$: neut. equiv., 150.2. Found: neut. equiv., 151.

5,11-Diaminopentadecane.—The 5,11-pentadecanedicarboxylic acid (386 g., 1.285 moles) was dissolved in 1250 ml. of concentrated sulfuric acid and 1650 ml. of benzene. Sodium azide (278 g., 4.28 moles) was added in portions with stirring, keeping the temperature between 35 and 40°. About eight hours was required for the addition. The reaction mixture was then heated at 45–50° for an hour, cooled and poured over ice. A solution of 2400 g. of sodium hydroxide in 5 liters of water was added with cooling to keep the temperature below 35°. The benzene layer was separated and the aqueous layer was extracted with ether. The combined extracts were washed with water and dried over magnesium sulfate. Distillation in a nitrogen atmosphere gave 294 g., 94.3%, of product boiling at 139–140° (0.6 mm.). This amine rapidly carbonates on exposure to the air.

Anal. Calcd. for $C_{15}H_{34}N_2$: N, 11.55. Found: N, 11.47.

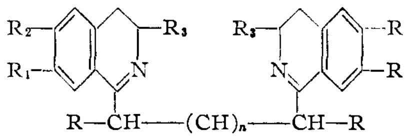
Table II



R	R₁	R₂	R₃	*n*	Formula	M.p., °C.	Method[a]	Rxn. time, hr.	Yield,[b] %	Nitrogen, % Calcd.	Nitrogen, % Found
H	OCH_3	OCH_3	CH_3	2	$C_{28}H_{40}N_2O_6$	174	A	3	90	5.60	5.27
C_2H_5	OCH_3	OCH_3	CH_3	4	$C_{34}H_{52}N_2O_6$	200–201	A	8	59	4.79	4.42
n-C_4H_9	OCH_3	OCH_3	CH_3	4	$C_{38}H_{60}N_2O_6$	193	A	39	26	4.37	4.00
H	OCH_3	OCH_3	CH_3	5	$C_{31}H_{46}N_2O_6$	98–102	A	3	88	5.17	5.30
n-C_4H_9	OCH_3	OCH_3	CH_3	5	$C_{39}H_{62}N_2O_6$	100–103	A	15	14	4.28	4.32
						107–115[c]	B	0.3	98.5	..	..
i-C_5H_{11}	OCH_3	OCH_3	CH_3	5	$C_{41}N_{66}N_2O_6$	107–109	A	15	50	4.11	4.06
n-C_4H_9	OCH_3	OCH_3	CH_3	6	$C_{40}H_{64}N_2O_6$	140–143	A	15	54	4.20	4.22
$C_6H_5CH_2CH_2$	OCH_3	OCH_3	CH_3	6	$C_{48}H_{64}N_2O_6$	170–171	A	5	78	3.67	3.61
C_2H_5	OCH_3	OCH_3	CH_3	10	$C_{40}H_{64}N_2O_5$	145–147	A	15	38	4.19	4.13
C_2H_5	OCH_3	OCH_3	H	4	$C_{32}H_{48}N_2O_6$	174–175	A	7	84	5.04	4.94
n-C_5H_{11}	OCH_3	OCH_3	H	4	$C_{38}H_{60}N_2O_6$	150–152	A	16	86	4.38	4.30
n-C_4H_9	OCH_3	OCH_3	H	5	$C_{37}H_{58}N_2O_6$	145[d]	A	15	81	4.48	4.63
						113–116[e]				..	4.59
						107–111[f]	B	0.3	93	..	..
i-C_5H_{11}	OCH_3	OCH_3	H	5	$C_{39}H_{62}N_2O_6$	109–110	A	16	73	4.28	4.19
n-C_4H_9	OCH_3	OCH_3	H	6	$C_{38}H_{60}N_2O_6$	152–154	A	15	84	4.38	4.50
C_2H_5	OCH_3	OCH_3	H	10	$C_{38}H_{60}N_2O_6$	157–160	B	1	100	4.38	4.66
$C_6H_5CH_2$	OCH_2O		H	4	$C_{40}H_{44}N_2O_6$	164–166	A	3	34	4.32	3.94
H	OCH_2O		H	5	$C_{27}H_{34}N_2O_6$	169–170	A	1	95	5.80	5.74
n-C_4H_9	OCH_2O		H	5	$C_{35}H_{50}N_2O_6$	163–165	B	1	89	4.71	4.81
n-C_4H_9	OCH_2O		H	6	$C_{36}H_{52}N_2O_6$	184–188	A	2.5	76	4.61	4.66
C_2H_5	OCH_2O		H	10	$C_{36}H_{52}N_2O_6$	170–171	B	1	99	4.61	4.72

[a] Method A, the amine and the acid were heated together at 180–200° in nitrogen atmosphere; method B, the diacid chloride was treated with the amine by Schotten–Baumann's method. [b] Based on crude yield. [c] M.p. of the crude product. [d] Higher melting isomer (18% yield). [e] Lower melting isomer (38% yield). [f] M.p. of the crude product.

Table III



R	R₁	R₂	R₃	*n*	Formula	M.p., °C.	Yield, %	Nitrogen, % Calcd.	Nitrogen, % Found
H	OCH_3	OCH_3	CH_3	2	$C_{28}H_{36}N_2O_4$	150–150.5	95.3	6.00	5.82
H	OCH_3	OCH_3	CH_3	2	$C_{28}H_{36}N_2O_4 \cdot 2CH_3I$	230–238 d.	100	3.75	3.61
n-C_4H_9	OCH_3	OCH_3	H	5	$C_{37}H_{54}N_2O_4 \cdot 2CH_3I$	120–130	86.5	3.20	3.01
n-C_4H_9	OCH_2O		H	5	$C_{35}H_{46}N_2O_4 \cdot 2CH_3I$	168–170 d.	92.5	3.33	3.21

N,N'-Dipiperonylidene-5,11-diaminopentadecane.—The diamine (260 g., 1.07 moles) and 338 g. (2.25 moles) of piperonal in three liters of absolute alcohol and 500 ml. of dry benzene were heated to reflux and one liter of distillate was removed through a 30-in. column over a period of two hours. The crystalline solid which separated on cooling the residue weighed 490 g. and melted at 105–107°. Concentration of the filtrate to one liter gave a second crop of 35 g. melting at 105–107°. The total yield was 525 g. or 97%.

Anal. Calcd. for $C_{31}H_{42}N_2O_4$: N, 5.52. Found: N, 5.46.

In some cases recrystallization from absolute alcohol was necessary in order to get material of proper melting point. By repeated fractional crystallization of the low-melting Schiff base isolated from the mother liquors from several preparations, it was possible to isolate a product having a constant melting point of 74–75.5°.

Anal. Calcd. for $C_{31}H_{42}N_2O_4$: N, 5.52. Found: N, 5.48.

N,N'-Dipiperonyl-5,11-diaminopentadecane.—The N,N'-dipiperonylidene-5,11-diaminopentadecane, m.p. 105–107°, 200 g., was made up to a volume of one liter with absolute alcohol in an 1800-ml. stainless steel hydrogenation bomb,[15] 15 g. of Raney nickel catalyst[6] was added and the mixture was reduced at an initial hydrogen pressure of 1000 lb./in.², first at room temperature with a final heating to 80°. Reduction was complete in two hours. The cooled reduction product was filtered and the alcohol was removed by distillation. The colorless residue was dissolved in 500 ml. of anhydrous ether and added with stirring and cooling to 500 ml. of isopropyl alcohol saturated with anhydrous hydrogen chloride. The crystalline solid which separated weighed 218 g., 95%, and melted at 178–180°. One recrystallization from absolute alcohol gave 213 g., 93%, of product which melted at 180–182°.

Anal. Calcd. for $C_{31}H_{48}Cl_2N_2O_4$: N, 4.80. Found: N, 4.78.

The Schiff base melting at 74–75.5°, 21.5 g., was similarly reduced in a 300-ml. bomb. Conversion of the reduced product to its dihydrochloride and recrystallization from a mixture of absolute alcohol and ethyl acetate gave a product melting at 175–176°; the melting point of its mixture with the higher-melting product was 163–165°.

Anal. Calcd. for $C_{31}H_{48}Cl_2N_2O_4$: N, 4.80. Found: N, 4.75.

N,N'-Dimethyl-N,N'-dipiperonyl-5,11-diaminopentadecane.—N,N'-Dipiperonyl-5,11-diaminopentadecane dihydro-

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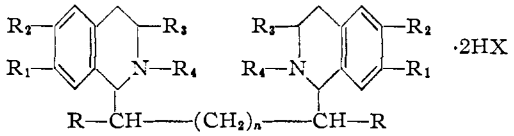
(15) American Instrument Co., Silver Spring, Md.

TABLE IV



R	R₁	R₂	R₃	R₄	n	X	Formula	M.p., °C.	Yield, %	Nitrogen, % Calcd.	Nitrogen, % Found
H	OCH₃	OCH₃	CH₃	H	2	Cl	$C_{28}H_{42}Cl_2N_2O_4$	270–270.5	..	5.17	4.87
H	OCH₃	OCH₃	CH₃	CH₃	2	I	$C_{30}H_{46}I_2N_2O_4$[a]	227–231	32.5	[b]	
								253–254	16.4	[c]	
C₂H₅	OCH₃	OCH₃	CH₃	H	4	Cl	$C_{34}H_{54}Cl_2N_2O_4$	*ca.* 170	97.0	4.48	4.31
C₂H₅	OCH₃	OCH₃	CH₃	CH₃	4	Cl	$C_{36}H_{58}Cl_2N_2O_4$	*ca.* 165	79.0	4.28	4.09
H	OCH₃	OCH₃	CH₃	H	5	Cl	$C_{31}H_{48}Cl_2N_2O_4$	255–256.5	88.2	4.80	4.67
n-C₄H₉	OCH₃	OCH₃	CH₃	H	5	Cl	$C_{39}H_{64}Cl_2N_2O_4$	160–180	55.0	4.03	3.97
i-C₅H₁₁	OCH₃	OCH₃	CH₃	H	5	Cl	$C_{41}H_{68}Cl_2N_2O_4$	150–170	55.0	3.87	3.81
n-C₄H₉	OCH₃	OCH₃	CH₃	H	6	Cl	$C_{40}H_{66}Cl_2N_2O_4$	*ca.* 170	77.5	3.95	4.03
C₂H₅	OCH₃	OCH₃	H	H	4	Cl	$C_{32}H_{50}Cl_2N_2O_4$	240–243	78.5	4.70	4.72
n-C₄H₉	OCH₃	OCH₃	H	H	5	Cl	$C_{37}H_{58}Cl_2N_2O_4$	*ca.* 210	91.5	4.20	4.29
i-C₅H₁₁	OCH₃	OCH₃	H	H	5	Cl	$C_{39}H_{64}Cl_2N_2O_4$	265–266	75.0	4.03	4.13
n-C₄H₉	OCH₃	OCH₃	H	H	6	Cl	$C_{38}H_{62}Cl_2N_2O_4$	260–264	Trace	4.11	4.01
C₂H₅	OCH₃	OCH₃	H	H	10	Cl	$C_{38}H_{62}Cl_2N_2O_4$	*ca.* 150	76.0	4.11	4.02
n-C₅H₁₁	OCH₂O		H	H	4	Cl	$C_{36}H_{54}Cl_2N_2O_4$	279–280 d.	Trace	4.31	4.52
H	OCH₂O		H	H	5	Cl	$C_{27}H_{36}Cl_2N_2O_4$	255	52.5	5.36	5.38
n-C₄H₉	OCH₂O		H	H	5	Cl	$C_{35}H_{52}Cl_2N_2O_4$	275–278 d.	12.0	4.43	4.48
								ca. 233 d.	66.0	4.43	4.30
n-C₄H₉	OCH₂O		H	CH₃	5	I	$C_{37}H_{58}I_2N_2O_4$	135–140	92.5	3.31	3.41
n-C₄H₉	OCH₂O		H	H	6	Cl	$C_{36}H_{54}Cl_2N_2O_4$[d]	258–260	26.7	4.32	4.10
								207–210	39.0	4.32	4.12
C₂H₅	OCH₂O		H	H	10	Cl	$C_{36}H_{54}Cl_2N_2O_4$[e]	254–255	25.5	4.32	4.36
								205	29.2	4.32	4.20

[a] Crude yield, 84%. Two products were isolated. [b] I, calcd. 33.8, found 33.9. [c] I, calcd. 33.8, found 33.6. [d] Crude yield, 77%; two products were obtained. [e] Crude yield, 99%; two products were isolated.

chloride (21.75 g., 0.0373 mole) was dissolved in hot water, the free base was precipitated by the addition of excess of 5% sodium hydroxide solution and after cooling was extracted with ether. The ether solution was washed with water, dried over magnesium sulfate and the ether was removed under vacuum. The free base, 19 g., was treated with 8.6 g. (0.187 mole) of 98–100% formic acid and 7 g. (0.08 mole) of 35% formalin with cooling. After the spontaneous reaction had slowed, the sirupy mixture was heated at reflux for 16 hours. The reaction mixture was poured over ice, and made strongly basic with 20% sodium hydroxide solution. The free base was extracted with ether, washed with water and dried over magnesium sulfate. Treatment of the ether solution with an excess of hydrogen chloride in ether precipitated a semi-solid hydrochloride. This was dissolved in hot isopropyl alcohol, concentrated to 75 ml. and diluted with 100 ml. of hot ethyl acetate. The crystalline solid which separated on cooling weighed 15.2 g., 67%, and melted at 142–144°.

Anal. Calcd. for $C_{33}H_{52}Cl_2N_2O_4$: N, 4.58. Found: N, 4.32.

N,N'-Di-(*p*-hydroxybenzyl)-5,12-diaminohexadecane.—To 100 ml. of 48% hydrobromic acid and 50 ml. of glacial acetic acid was added 12 g. of N,N'-di-(*p*-methoxybenzyl)-5,12-diaminohexadecane dihydrochloride and the mixture was refluxed for four hours. The acetic acid was removed by distillation. On cooling the residue a thick brown sirup separated. The aqueous layer was poured off and the sirup was partially dried by heating in a water-bath under vacuum, dissolved in hot isopropyl alcohol and dried over magnesium sulfate. The dried solution was concentrated to 100 ml. and diluted with 100 ml. of hot ethyl acetate. The crystalline product which separated weighed 9.7 g., 71%, and melted at 180–182°.

Anal. Calcd. for $C_{30}H_{50}Br_2N_2O_2$: N, 4.44. Found: N, 4.42.

N,N'-Di-[3-(*p*-methoxyphenyl)-propyl]-5,11-diamino-2,14-dimethylpentadecane.—There was dissolved in 130 ml. of absolute alcohol 10.5 g. (0.061 mole) of *p*-methoxycinnamaldehyde and 8.1 g. (0.03 mole) of 5,11-diamino-2,14-dimethylpentadecane and the solution was allowed to stand overnight. A crystalline Schiff base separated. The suspension was transferred to a 300-ml. hydrogenation bomb, 3 g. of Raney nickel catalyst was added and the mixture was reduced at an initial hydrogen pressure of 1100 lb./in.² at room temperature with gradual heating to 80°. Removal of catalyst and solvent and precipitation of the product as a dihydrochloride from ether with ethereal hydrogen chloride gave a semi-solid product. This was dissolved in hot absolute alcohol, 75 ml., diluted with 100 ml. of hot ethyl acetate and let stand. A crystalline product slowly separated. This weighed 14.6 g., 76%, and melted at 233–236°.

Anal. Calcd. for $C_{37}H_{64}Cl_2N_2O_2$: N, 4.38. Found: N, 4.34.

N,N'-Di-[3-(*p*-methoxyphenyl)-propyl]-1,6-diaminohexane.—A mixture of 3.36 g. (0.029 mole) of 1,6-diaminohexane and 10.5 g. (0.585 mole) of 3-(*p*-methoxyphenyl)-propionic acid was placed in a 50-ml. flask and heated in an oil-bath at 200° for one hour. The crude amide which formed was recrystallized twice from methanol. There was obtained 10 g. of product, 83.5%, melting at 187–188.5°.

Anal. Calcd. for $C_{26}H_{36}N_2O_4$: N, 6.35. Found: N, 6.30.

The diamide (10 g., 0.0228 mole) was placed in a sintered glass Soxhlet extraction tube and was extracted over a period of 40 hours into a solution of 4 g. (0.105 mole) of lithium aluminum hydride in 350 ml. of tetrahydrofuran. The reaction mixture was decomposed by the cautious addition of 4 ml. of water followed by 3 ml. of 20% sodium hydroxide and 14 ml. of water. The precipitated solids were removed by filtration and washed with ether. The solvents were removed from the filtrate by distillation under vacuum and the residue was dissolved in ether, washed with water, and on attempted extraction with 5% hydrochloric acid a crystalline product separated. This was filtered and crystallized from 50% aqueous isopropyl alcohol, yield 10.5 g. One more recrystallization from the same solvent gave 8.3 g. of product, 76%, which melted at 298–302°.

Anal. Calcd. for $C_{26}H_{42}Cl_2N_2O_2$: N, 5.77. Found: N, 5.83.

N,N'-Bis-(homoveratryl)-5,11-pentadecanedicarboxamide. Method A.—A mixture of 36.2 g. (0.2 mole) of homoveratrylamine and 30.0 g. (0.1 mole) of 5,11-pentadecanedicarboxylic acid (m.p. 90–91°) was heated at 195–200° for 15 hours in a dry nitrogen atmosphere to give a dark red melt which after cooling was poured into 500 ml. of ether. A light pink solid separated, was collected, washed with ether and dried *in vacuo;* yield 50.5 g., 81.0%, m.p. 108–115°. It was recrystallized ten times from acetone to give 9.4 g. of a white solid melting at 145° (softening at 124°); λ_{max} 230.5 mμ (log ϵ 4.18), 283 (3.83).

Anal. Calcd. for $C_{37}H_{58}N_2O_6$: N, 4.48. Found: N, 4.60.

All of the filtrates were combined, concentrated and diluted with ether to give 19.2 g. of a white solid melting at 113–116° after one recrystallization from acetone–hexane; λ_{max} 230 mμ (log ϵ 4.23), 283 (3.81).

Anal. Calcd. for $C_{37}H_{58}N_2O_6$: N, 4.48. Found: N, 4.53.

Method B.—A crude 5,11-pentadecanedicarboxylic acid chloride was prepared from 150 g. (0.5 mole) of the corresponding dicarboxylic acid by refluxing in 100 ml. of thionyl chloride for 3 hours, followed by removing excess thionyl chloride at a water-pump. To an ice-cold mixture of 192.8 g. (1.07 moles) of homoveratrylamine in 500 ml. of ether and 500 ml. of 10% sodium hydroxide solution was added dropwise during 20 minutes the dicarboxylic acid chloride in 250 ml. of ether with vigorous stirring to cause immediate separation of a white solid. The reaction mixture was kept at room temperature overnight. The solid was collected by suction, washed with water and ether, and dried at 50° in an oven; yield 290.2 g., 93.0%, m.p. 107–111°.

5,11-Bis-(6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolyl)-pentadecane Dihydrochloride.—A solution of 55.7 g. (0.089 mole) of the above bis-amide in 100 ml. of phosphoryl chloride was refluxed for 1.5 hours and excess chloride was removed *in vacuo* at a water-pump to give a sirupy bis-dihydroisoquinoline. It was added to ice-water, made basic with concd. ammonium hydroxide and the resulting free base was extracted with ether and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the residue was dissolved in 200 ml. of methanol and hydrogenated with 0.5 g. of Adams catalyst under 50 lb. pressure of hydrogen. The calculated amount of hydrogen was absorbed in 3 hours. The solvent was distilled off and the residue was taken up in ether. The ethereal solution was added to ether saturated with dry hydrogen chloride to give a tan sirupy hydrochloride which was washed with ether, dissolved in methanol and then evaporated to dryness *in vacuo* at 100° to give a pale yellow powder, yield of 54.0 g., 91.5%. A sample was dried at 140° (0.1 mm.) for an hour for analysis. It melted at about 210° with softening at 145°.

Anal. Calcd. for $C_{37}H_{58}Cl_2N_2O_4$: N, 4.20; Cl, 13.2. Found: N, 4.29; Cl, 13.3.

1,4-Bis-(3-methyl-6,7-dimethoxy-3,4-dihydro-1-isoquinolyl)-butane.—N,N'-Bis-(α-methylhomoveratryl)-1,4-butanedicarboxamide was prepared in 90% yield by heating 39.0 g. (0.2 mole) of α-methylhomoveratrylamine and 14.6 g. (0.1 mole) of adipic acid at 180° for 3 hours. The crude diamide weighed 41.0 g., m.p. 142–155°. The diamide (9.3 g.) was dissolved in 30 ml. of phosphoryl chloride and the solution was refluxed for 20 minutes. It was dissolved in ice-water and made basic with concd. ammonium hydroxide to give 8.0 g., 93%, of a white powder melting at 149–150°. A sample was once recrystallized from aqueous methanol to give a powder of m.p. 150.5°; λ_{max} 230 mμ (log ϵ 4.16), 276.5 (3.80), 312.5 (3.82).

Anal. Calcd. for $C_{28}H_{36}N_2O_4$: N, 6.00. Found: N, 5.82.

5,11-Bis-(6,7-methylenedioxy-3,4-dihydro-1-isoquinolyl)-pentadecane Dimethiodide.—N,N'-Bis-(homopiperonyl)-5,11-pentadecanedicarboxamide (27.3 g., 0.046 mole) was added to 100 ml. of phosphoryl chloride and the mixture was refluxed for 2 hours to give a greenish-yellow solution. Excess phosphoryl chloride was removed at a water-pump. The remaining sirup was added to *ca.* 100 ml. of methanol to give a clear solution which was made basic with concd. ammonium hydroxide. The resulting free base was taken up in ether and dried over anhydrous magnesium sulfate. The solvent was removed at a water-pump to leave a sirup to which was added 50 ml. of methyl iodide. The resulting clear yellowish orange solution was refluxed for an hour to give a deep yellow pasty mixture. Excess methyl iodide was removed *in vacuo* at 100° to give a bright yellow solid mass, yield of 35.8 g., 92.5%, m.p. 168–170° dec. after two recrystallizations from isopropyl alcohol; λ_{max} 223 mμ (log ϵ 4.52), 254 (4.36), 310 (4.05), 373 (4.16).

Anal. Calcd. for $C_{37}H_{52}I_2N_2O_4$: N, 3.33. Found: N, 3.21.

5,11-Bis-(2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydro-1-isoquinolyl)-pentadecane Dihydroiodide.—The dimethiodide (14 g., 0.017 mole) was dissolved in 200 ml. of methanol and hydrogenated with 0.3 g. of Adams catalyst. The calculated amount of hydrogen was absorbed in 2 hours. The filtrate was evaporated to dryness *in vacuo* at 100° to give a pale pink solid, yield of 13.0 g., m.p. *ca.* 120° with foaming (softening began at 108°). It was dissolved in hot isopropyl alcohol (Norit) and then evaporated to dryness at a water-pump to give a pale pink solid of m.p. 135–140° (after drying at 140° *in vacuo*), yield 11.7 g., 83%; λ_{max} 222.5 mμ (log ϵ 4.46), 296 (3.92).

Anal. Calcd. for $C_{37}H_{58}I_2N_2O_4$: N, 3.31. Found: N, 3.41.

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