TABLE III

CARBONYL AND IMINO INFRARED ABSORPTION BANDS[a-c]

Compd.	C=O, μ	C=N, μ
I	5.78, 5.85	6.17
II[d]	5.80, 5.88	...
III	5.82	6.19
IV	5.70, 5.77	6.15
V	5.73, 5.91	6.12
VI	5.76	6.17
VII	5.80	6.18
VIII	5.67, 5.74	6.22
IX	5.77	6.21
X	5.77	6.21
XI	5.83	6.16
XII	5.79	6.20
XIII	5.81	6.17
XIV	5.78, 5.84	6.16
XV	5.80, 5.85	6.19
XVI	5.66, 5.73	6.04
XVII	5.82, 5.86	6.08
XVIII	5.80, 5.86	6.16
XIX	5.82, 5.87	6.15

[a] All spectra were obtained using KBr plates. [b] The presence of two carbonyl bands indicates a mixture of monomer and dimer in the solid state. On the basis of earlier work [see L. J. Bellamy, "The Infared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958; E. J. Hartwell, R. E. Richards, and H. W. Thompson, *J. Chem. Soc.*, 1436 (1948); M. St. C. Flett, *ibid.*, 962 (1951)] the lower wave-length band has been assigned to the carbonyl absorption of the monomer while the higher wave-length band has been assigned to the carbonyl absorption of the dimer. [c] F. Mathis, *Compt. Rend.*, **232**, 505 (1961), reported that infrared absorption bands due to oxime imino groups lie in the 5.95–6.20 μ region. His studies indicated that aromatic oximes absorbed at higher wave lengths than did the aliphatic oximes. The same effect was observed in this work on oxime ethers. [d] An imino band in the 6-μ region was not observed.

5-Nitro-2-furfural.[10]—This compound was used without purification.

2-Phenylcyclopentanone.—Van Zoeren's method[11] for the synthesis of 2-(2-thienyl)cyclopentanone was employed. A 45% yield of product was obtained which boiled at 145–148° (16 mm.), $n^{23}D$ 1.5515.

Ethyl Aminooxyacetate.—The method described by Frank and Riedl[7] for the preparation of methyl aminooxyacetate was employed here. The product was an oil; yield, 53%; $n^{25}D$ 1.4267. The hydrochloride salt melted at 115–117°.

Anal. Calcd. for $C_4H_9NO_3 \cdot HCl$: C, 30.88; H, 6.48; N, 9.00. Found: C, 30.96; H, 6.29; N, 9.02.

Aminooxyacetic Acid Derivatives. Method A.—A solution of the aldehyde or ketone and 1 equiv. of aminooxyacetic acid hemihydrochloride (Eastman) was made in about 25 times its weight of 90% ethanol. To the solution was added 3.3 equiv. of sodium acetate. The mixture was stirred and refluxed for 2 hr. The solvent was then evaporated *in vacuo*. The residue was slurried in an equal volume of water and made alkaline with 10% aqueous sodium hydroxide solution. The unchanged aldehyde or ketone was removed by filtration or by extraction with ether. The aqueous phase was then made acidic to congo red indicator paper and the product was isolated by filtration or by extraction with ether and recrystallized.

Method B.—To a solution of the aldehyde or ketone and 1 equiv. of aminooxyacetic acid hemihydrochloride in 90% ethanol (as in A) was added 1 equiv. of triethylamine and the solution was refluxed for 2 hr. The solvent was removed *in vacuo*. The residue was then washed with water and recrystallized.

Method C.—Benzene was substituted for 90% ethanol as the solvent, but the procedure outlined for B was otherwise employed. The reaction mixture was heterogenous during the entire reaction period.

(10) H. Gilman and G. F. Wright, *J. Am. Chem. Soc.*, **52**, 2550 (1930).

(11) G. J. Van Zoeren, U. S. Patent 2,520,516 (1950); *Chem. Abstr.*, **45**, 647*d* (1951).

Method D.—Aminooxyacetic acid hemihydrochloride was allowed to react with 9-anthraldehyde (Aldrich) (12.3 g.) according to B. A yellow solid (4.2 g.) was isolated which melted at 188–190° dec., but the elemental analyses ($C_{38}H_{32}N_4O_3$), after two recrystallizations from ethanol, indicated that it was not the desired product. This material (3 g.) was refluxed for 5 hr. in 50 ml. of 1.4 *N* ethanolic hydrogen chloride. The solution was filtered and evaporated *in vacuo*. The residue was recrystallized twice from petroleum ether (b.p. 60–90°) and there resulted 1.1 g. of yellow needles which fluoresced blue, m.p. 69–70°. This material analyzed correctly as the ethyl ester of the desired product.

Method E.—A solution of the aldehyde and 1 equiv. of ethyl aminooxyacetate in about 25 times its weight of absolute ethanol was refluxed for 2 hr. The solvent was removed *in vacuo* and the residue was recrystallized.

Acknowledgments.—The author is indebted to Mrs. Janice Hall and Mr. William F. Boyd who ran the infrared spectra, and to Mr. Martin Gordon and Mr. Raymond Snider who performed the microanalyses. The author's appreciation is also extended to Mr. John Schaar who prepared the 2-phenylcyclopentanone.

Agents Affecting Lipid Metabolism. XII. N,N′-Disubstituted Cyclohexane-1,4-bis(methylamines)[1]

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The discovery of potent cholesterol biosynthesis inhibitory activity in compounds related to N,N′-dibenzylethylenediamine[2] has led to the synthesis of *trans*-1,4-bis(2-chlorobenzylaminomethyl)cyclohexane, whose biological properties have already been described.[3] We wish to report here, the synthesis of this compound and of a variety of related symmetrical compounds which retain the cyclohexane-1,4-bis(methylamine) moiety. Tables I and II describe these compounds, and Tables III and IV describe intermediates used in their preparation.

Experimental[4]

Method A. N,N′-Di(2-chlorobenzylidine)cyclohexane-*trans*-1,4-bis(methylamine).—2-Chlorobenzaldehyde (28.4 g., 0.2 mole) and cyclohexane-*trans*-1,4-bis(methylamine) (14.2 g., 0.1 mole) were refluxed in benzene solution (300 ml.) until the theoretical volume of water had been collected in a Dean–Stark trap (*ca.* 3 hr.). The benzene was removed *in vacuo*, and the residue was crystallized from benzene. It had m.p. 150–154° (38.0 g.), λ_{max} 250 mμ (ε 31,300), $\nu_{max}^{CHCl_3}$ 1640 cm.$^{-1}$.

Anal. Calcd. for: $C_{22}H_{24}Cl_2N_2$: Cl, 18.31. Found: Cl, 17.92.

N,N′-Di(2-chlorobenzyl)cyclohexane-*trans*-1,4-bis(methylamine) (Table I, 4).—The above bis Schiff base (37.0 g.) was suspended in methanol (500 ml.) and sodium borohydride (7.5 g.) was added portionwise at a rate permitting gentle reflux. The mixture became homogeneous as the reduction proceeded. After refluxing for 16 hr., the methanol was removed *in vacuo* and the residue was distributed between chloroform and water. The chloroform layer was washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to yield the product (35.5 g.) as a solid, m.p. 101–103° (ethanol). The dihydrochloride salt was prepared in methanol solution with methanolic hydrogen chloride. Crystallization yielded analytically pure material.

(1) For Part XI of this series see: D. Dvornik, M. Kraml, and J. F. Bagli, *J. Am. Chem. Soc.*, **86**, 2739 (1964).

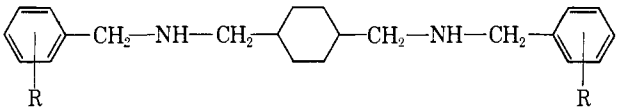
(2) M. Kraml, L. G. Humber, J. Dubuc, and R. Gaudry, *J. Med. Chem.*, **7**, 500 (1964).

(3) (a) D. Dvornik, M. Kraml, J. Dubuc, and R. Gaudry, *J. Am. Chem. Soc.*, **85**, 3309 (1963); (b) C. Chappel, J. Dubuc, D. Dvornik, M. Givner, L. Humber, M. Kraml, K. Voith, and R. Gaudry, *Nature*, **201**, 497 (1964).

(4) Melting points were taken on a Thomas-Hoover apparatus and are corrected. Analyses were done by Mr. W. Turnbull and staff of our laboratories.

TABLE I

N,N'-DIBENZYL DERIVATIVES OF CYCLOHEXANE-1,4-BIS(METHYLAMINE)[a]



No.	R	M.p., °C.	Recryst. Solvent	Formula	% N Calcd.	% N Found	% Cl Calcd.	% Cl Found
1	...[b]	358 dec.	*c*	$C_{22}H_{30}N_2 \cdot 2HCl$[d]	...	...	17.93	17.84
2	...[e]	307 dec.	*f,g*	$C_{22}H_{30}N_2 \cdot 2HCl$[h]	...	...	17.93	17.64
3	2-Chloro	286–288	*f,g*	$C_{22}H_{28}Cl_2N_2 \cdot 2HCl$	6.03	5.80	30.54	30.54
4	2-Chloro[b]	298–300	*f,g*	$C_{22}H_{28}Cl_2N_2 \cdot 2HCl$	6.03	5.87	30.54	30.45
5	2-Chloro[e]	232–234	*f,g*	$C_{22}H_{28}Cl_2N_2 \cdot 2HCl$[i]	...	...	30.54	30.31
6	3-Chloro	314–315	*c,j*	$C_{22}H_{28}Cl_2N_2 \cdot 2HCl$	6.03	5.77	30.54	30.32
7	4-Chloro	>360	*f,g*	$C_{22}H_{28}Cl_2N_2 \cdot 2HCl$	6.03	5.87	30.54	30.38
8	2,6-Dichloro	263–264	*f,g*	$C_{22}H_{26}Cl_4N_2 \cdot 2HCl$	5.25	5.11	39.87	39.75
9	2,4-Dichloro	308–309	*f,g*	$C_{22}H_{26}Cl_4N_2 \cdot 2HCl$	5.25	5.11	39.87	39.78
10	3,4-Dichloro	328–330	*k*	$C_{22}H_{26}Cl_4N_2 \cdot 2HCl$	5.25	5.13	39.87	39.54
11	2-Bromo[b]	286–288	*f,g*	$C_{22}H_{28}Br_2N_2 \cdot 2HCl$	5.06	4.80	12.82	12.76
12	2-Bromo[e]	218–220	*f,g*	$C_{22}H_{28}Br_2N_2 \cdot 2HCl$	5.06	4.95	12.82	12.70
13	3-Bromo	312	*f*	$C_{22}H_{28}Br_2N_2 \cdot 2HCl$	5.06	5.16	12.82	13.13
14	4-Bromo	>360	*c*	$C_{22}H_{28}Br_2N_2 \cdot 2HCl$	5.06	4.72	12.82	12.84
15	2-Fluoro[b]	301–302	*c*	$C_{22}H_{28}F_2N_2 \cdot 2HCl$[l]	...	...	16.44	16.31
16	2-Fluoro[e]	246–248	*f,g*	$C_{22}H_{28}F_2N_2 \cdot 2HCl$[m]	...	...	16.44	16.31
17	3-Fluoro	336–337	*f*	$C_{22}H_{28}F_2N_2 \cdot 2HCl$	6.49	6.44	16.44	16.49
18	4-Fluoro	364–365	*f*	$C_{22}H_{28}F_2N_2 \cdot 2HCl$	6.49	6.38	16.44	16.65
19	2-Methyl	320 dec.	*f,g*	$C_{24}H_{34}N_2 \cdot 2HCl$	6.61	6.75	16.74	16.63
20	4-Methyl	357–358	*c,f*	$C_{24}H_{34}N_2 \cdot 2HCl$	6.61	6.31	16.74	16.75
21	4-Isopropyl	321–322	*f*	$C_{28}H_{42}N_2 \cdot 2HCl$	5.84	5.72	14.80	15.06
22	2,4,6-Trimethyl	>360	*f,g*	$C_{28}H_{42}N_2 \cdot 2HCl$	5.84	5.65	14.80	14.49
23	2-Chloro-5-methyl	275–276	*f,g*	$C_{24}H_{32}Cl_2N_2 \cdot 2HCl$	...	...	28.80	27.92
24	2-Chloro-6-methyl	>360	*c,j*	$C_{24}H_{32}Cl_2N_2 \cdot 2HCl$	5.69	5.59	28.80	28.76
25	2-Methoxy	250–252	*j*	$C_{24}H_{34}N_2O_2 \cdot 2HCl$	6.15	6.39	15.57	15.32
26	2,3-Dimethoxy	235 dec.	*f,g*	$C_{26}H_{38}N_2O_4 \cdot 2HCl$	...	...	13.76	14.19
27	3,4-Dimethoxy	239–241	*f,g*	$C_{26}H_{38}N_2O_4 \cdot 2HCl$	5.43	5.45	13.76	13.89
28	3,4,5-Trimethoxy	248–249	*f*	$C_{28}H_{40}N_2O_6 \cdot 2HCl$	4.89	5.02	12.36	12.27
29	3,4-Dibenzyloxy	186–188	*f,g*	$C_{50}H_{54}N_2O_2 \cdot 2HCl$	3.42	3.55	8.64	8.69
30	2-Hydroxy	146–149	*f*	$C_{22}H_{30}N_2O_2$[n,o]	...	...	...	...
31	2-Nitro	259–260	*g,j*	$C_{22}H_{28}N_4O_4 \cdot 2HCl$	11.54	11.64	14.61	14.27
32	2-Amino	197 dec.	*j*	$C_{22}H_{32}N_4 \cdot 2C_4H_4O_4$[p,q]	9.58	9.61	...	...
33	2-Methylthio	271–272	*f,g*	$C_{24}H_{34}N_2S_2 \cdot 2HCl$	5.74	5.47	14.54	14.30
34	4-Acetamido	>360	*c*	$C_{26}H_{36}N_4O_2 \cdot 2HCl$	10.99	10.78	13.91	13.65
35	4-Dimethylamino	>360	*g,j*	$C_{26}H_{40}N_4 \cdot 4HCl$	10.10	9.97	25.57	25.20
36	2-Trifluoromethyl[b]	265–269	*f*	$C_{24}H_{28}F_6N_2 \cdot 2HCl$	5.27	5.38	13.34	13.15

[a] These compounds are mixtures of *cis* and *trans* isomers unless otherwise indicated and were prepared by method A (see Experimental) except for **33** which was prepared by method B, and **32** which was obtained by reducing **31** with Raney nickel in ethanol at atmospheric pressure and room temperature. [b] This compound is a 1,4-*trans* isomer. [c] Water. [d] Calcd.: C, 66.83; H, 8.16. Found: C, 67.19; H, 8.27. [e] This compound is a 1,4-*cis* isomer. [f] Methanol. [g] Ether. [h] Calcd.: C, 66.83; H, 8.16. Found: 67.10; H, 8.26. [i] Calcd.: C, 56.89; H, 6.51. Found: C, 56.63; H, 6.66. [j] Ethanol. [k] Triturated with hot methanol. [l] Calcd.: F, 8.81. Found: F, 8.67. [m] Calcd.: F, 8.81. Found: F, 8.67. [n] Calcd.: C, 74.54; H, 8.53. Found: C, 74.74; H, 8.57. [o] The diacetate salt has m.p. 195–196° (methanol–ether). [p] A diacid maleate salt. [q] Calcd.: C, 61.61; H, 6.89. Found: C, 62.40; H, 6.90.

This method was used for the synthesis of most of the compounds of Table I and for some of the compounds of Table II (see tables for exceptions). The cyclohexane-1,4-bis(methylamine) used was the *trans*, *cis*, or a mixture of isomers as required and was commercially available. The intermediate Schiff bases generally were not characterized by melting point or by elemental analysis but were used as the crude products. Most of the aldehydes required are described in the literature and were commercially available. The following aldehydes have not been previously reported.

2-Chloro-5-methylbenzaldehyde.—This compound was prepared from 2-chloro-5-methylaniline in 34% yield by the method of Jolad and Rajagopal.[5] The semicarbazone derivative had m.p. 248–250°.

Anal. Calcd. for: $C_9H_{10}ClN_3O$: Cl, 16.75. Found: Cl, 16.72.

2-Chloro-6-methylbenzaldehyde was prepared in 31% yield from the corresponding aniline and had b.p. 74° (0.4 mm.). The semicarbazone had m.p. 234–236° dec.

Anal. Calcd. for $C_9H_{10}ClN_3O$: Cl, 16.75. Found: Cl, 16.58.

2-Trifluoromethylbenzaldehyde was prepared in 20% yield from the corresponding acid chloride by reduction with lithium tri-*t*-butoxyaluminum hydride in diglyme at −78°.[6] It was purified through the bisulfite adduct and had b.p. 28–38° (0.3–0.6 mm.) and $\nu_{max}^{CHCl_3}$ 1700 cm.$^{-1}$.

Method B.—Most of the compounds of Table II were prepared by reduction of the diamides of Tables III and IV. The diamide was added to a suspension of an equal weight of lithium aluminum hydride in anhydrous tetrahydrofuran (20 ml./g. of diamide). The mixture was refluxed with stirring for 24 hr., cooled, and the excess reagent was destroyed by the cautious addition of water. The diamines were converted to their disalts by the usual procedures and were crystallized to analytical purity.

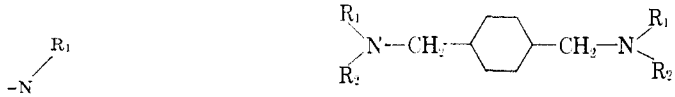
Method C. N,N'-Dibutyrylcyclohexane-*trans*-1,4-bis(methylamine) (Table III, 3).—Butyryl chloride (25 g., 0.236 mole) in benzene was added dropwise to a solution of cyclohexane-*trans*-1,4-bis(methylamine) (14.2 g., 0.1 mole) in water (100 ml.)

(5) S. D. Jolad and S. Rajagopal, *Naturwiss.*, **48**, 645 (1961).

(6) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **80**, 5377 (1958).

TABLE II

N,N′-DI(ARALKYL AND NONAROMATIC) DERIVATIVES OF CYCLOHEXANE-1,4-BIS(METHYLAMINE)[a]



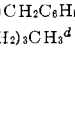
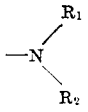
No.	R₁, R₂	M.p., °C.	Recrystn. solvent	Method	Formula	% N Calcd.	% N Found	% Cl Calcd.	% Cl Found
1	NH_2	>320	*h*	*c*	$C_8H_{18}N_2 \cdot 2HCl$	...	...	32.95	32.69
2	$NHCH_3$	>310	*h*	B (III)	$C_{10}H_{22}N_2 \cdot 2HCl$	11.52	11.27	29.15	29.13
3	NHC_2H_5	>310	*h*	B (III)	$C_{12}H_{26}N_2 \cdot 2HCl$	10.53	9.90	26.14	26.15
4	$NH(CH_2)_3CH_3$[d]	>310	*h*	B (III)	$C_{16}H_{34}N_2 \cdot 2HCl$	8.56	8.60	21.66	22.25
5	$NHCH_2CH(CH_3)_2$	>310	*c*	A	$C_{16}H_{34}N_2 \cdot 2HCl$	8.56	8.54	21.66	21.70
6	$NH(CH_2)_2CH(CH_3)_2$	>310	*e*	A	$C_{18}H_{38}N_2 \cdot 2HCl$	7.88	7.77	19.95	19.92
7	$NH(CH_2)_6CH_3$[d]	>310	*e*	B (III)	$C_{22}H_{46}N_2 \cdot 2HCl$	6.81	6.81	17.23	17.21
8	$NH(CH_2)_3CH(CH_3)CH{=}C(CH_3)_2$[f]	>310	*e*	A	$C_{28}H_{54}N_2 \cdot 2HCl$	5.70	5.79	14.42	14.67
9	$NH(CH_2)_3CH(CH_3)CH_2CH(CH_3)_2$	>310	*b*	*g*	$C_{28}H_{58}N_2 \cdot 2HCl$	5.65	5.69	14.31	14.16
10		>360	*b*	A	$C_{22}H_{36}N_2 \cdot 2HCl$	6.94	7.26	17.58	17.43
11	$NHCH_2C_6H_{11}$[h,d]	>360	*b*	A, B (III)	$C_{22}H_{40}N_2 \cdot 2HCl$	6.88	6.89	17.40	17.38
12	$NHCH_2C_6H_{11}$[h,i]	>360	*b*	B (III)	$C_{22}H_{40}N_2 \cdot 2HCl$	6.88	6.91	17.40	17.62
13	$NHCH_2C_4H_7$[j,d]	>310	*b,k*	B (III)	$C_{18}H_{34}N_2 \cdot 2HCl$	7.97	7.92	20.18	20.14
14	$NHCH_2C_6H_9$[l]	>310	*e*	B (III)	$C_{20}H_{38}N_2 \cdot 2HCl$	7.38	7.29	18.69	18.62
15	 [d]	>310	*b,m*	B (IV)	$C_{24}H_{38}N_2 \cdot 2HCl$	6.56	6.66	16.59	16.63
16	 [d]	>310	*e*	*n*	$C_{24}H_{42}N_2 \cdot 2HCl$	6.49	6.60	16.43	16.41
17	 [d]	161–163	*b,m*	B (III)	$C_{22}H_{38}N_2 \cdot 2CH_3COOH$[o]	...	...	...	...
18	$NH(CH_2)_2C_6H_{11}$[h,d]	>310	*e*	B (III)	$C_{24}H_{46}N_2 \cdot 2HCl$	6.43	6.76	16.28	16.15
19	$NH(CH_2)_3C_6H_{11}$[h]	>310	*b*	B (III)	$C_{26}H_{50}N_2 \cdot 2HCl$	6.03	6.39	15.30	15.23
20	 [d]	315 dec.	*p,q*	B (IV)	$C_{24}H_{38}N_2O_2 \cdot 2HCl$	6.82	6.69	17.23	17.17
21	$NHC(CH_3)_3$[d]	>310	*b,m*	B (IV)	$C_{16}H_{34}N_2 \cdot 2HCl$[p]	...	...	16.13	14.91
22	$NHC(CH_3)_2CH_2C(CH_3)_3$[d]	>310	*b,m*	B (IV)	$C_{24}H_{50}N_2 \cdot 2HCl$[r]	8.56	8.21	21.66	20.91
23	NHC_5H_9[l,d]	>310	*b,m*	A	$C_{12}H_{34}N_2 \cdot 2HCl$	7.97	7.98	20.16	19.98
24	NHC_6H_{11}[h,d]	>360	*s*	A, B (IV)	$C_{26}H_{38}N_2 \cdot 2HCl$	7.38	7.36	18.69	18.82
25	NHC_7H_{13}[t,d]	>360	*b*	B (IV)	$C_{22}H_{42}N_2 \cdot 2HCl$	6.88	7.09	17.40	17.55
26	NHC_8H_{15}[u,d]	186–188	*s*	A	$C_{24}H_{46}N_2 \cdot 2CH_3COOH$[v]	...	...	...	...
27	 [d]	>320	*b,m*	A	$C_{22}H_{38}N_2 \cdot 2HCl$	6.94	7.01	17.58	17.47
28	 [d]	195–197	*b,m*	A	$C_{22}H_{42}N_2 \cdot 2CH_3COOH$[w]	...	...	...	...
29	 [d]	>320	*e*	A	$C_{22}H_{42}N_2 \cdot 2HCl$	6.87	6.94	17.41	17.37
30	 [d]	94–96	*q*	A	$C_{26}H_{46}N_4$[x]	16.66	16.93	...	...
31	 [d]	137–141[y]	*z*	A	$C_{20}H_{38}N_2O_2$[aa]	8.28	8.31	...	...
32	 [d]	191–197[bb]	*b*	A	$C_{20}H_{38}N_2O_2$[cc]	8.28	8.26	...	...
33	C_4H_8N[d,dd]	>360	*s*	B (IV)	$C_{16}H_{30}N_2 \cdot 2HCl$	8.67	8.47	21.93	22.04
34	$C_5H_{10}N$[d,ee]	>360	*b*	B (IV)	$C_{18}H_{34}N_2 \cdot 2HCl$[ff]	...	...	...	...
35	$C_6H_{12}N$[d,gg]	358 dec.	*b*	B (IV)	$C_{20}H_{40}N_2 \cdot 2HCl$	7.35	7.13	18.59	18.59
36	$N(CH_3)CH_2C_6H_5$[d]	248 dec.	*m,s*	*hh*	$C_{24}H_{34}N_2 \cdot 2HCl$	6.61	6.36	16.74	16.12
37	 [d]	213–215	*b,m*	B (III)	$C_{30}H_{44}Cl_2N_2 \cdot 2HCl$	4.86	4.77	24.60	24.45
38	$C_9H_{10}N$[ii,d]	342	*b*	B (IV)	$C_{26}H_{34}N_2 \cdot 2HBr$[jj]	5.22	5.40	...	...
39	 [d]	162–163	*z*	*kk*	$C_{28}H_{36}Cl_2N_2O_4$	5.23	5.17	13.24	13.32
40	NHC_9H_9[d,ll]	>310	*p*	B (IV)	$C_{26}H_{34}N_2 \cdot 2HCl$	6.26	6.27	15.84	15.80
41	NHC_9H_9[d,mm]	126–127	*z*	B (IV)	$C_{26}H_{34}N_2$[nn]	7.48	7.41	...	...
42	$NH(CH_2)_2C_6H_5$	>360	*e*	*oo*	$C_{24}H_{34}N_2 \cdot 2HCl$	...	...	16.74	16.82
43	$NHCH(CH_3)CH_2C_6H_5$	>360	*b,p*	A	$C_{26}H_{30}N_2 \cdot 2HCl$	6.20	5.92	15.70	15.48
44	$NHCH_2CH(CH_3)C_6H_5$	291–292	*b*	A	$C_{26}H_{30}N_2 \cdot 2HCl$	6.20	6.19	15.70	15.74
45	$NH(CH_2)_2OC_6H_5$	295–296	*e*	A	$C_{24}H_{34}N_2O_2 \cdot 2HCl$	6.15	6.18	15.57	15.40
46	$NHCH_2C_{10}H_7$[pp]	355 dec.	*p*	A	$C_{30}H_{34}N_2 \cdot 2HCl$	5.65	5.62	14.31	13.89
47	$NHCH_2C_{10}H_7$[qq]	>360	*b,m*	A	$C_{30}H_{34}N_2 \cdot 2HCl$	5.65	5.45	14.31	14.10
48	$NHCH_2C_4H_3O$[rr]	264	*b,m*	A	$C_{18}H_{26}N_2O_2 \cdot 2HCl$	7.46	7.60	18.89	19.02
49	$NHCH_2C_4H_3S$[ss]	>360	*b*	A	$C_{18}H_{26}N_2S_2 \cdot 2HCl$	6.88	6.83	17.40	17.51

TABLE II (*Continued*)

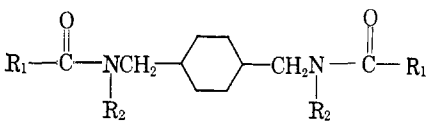


No.	M.p., °C.	Recrystn. solvent	Method	Formula	% N Calcd.	% N Found	% Cl Calcd.	% Cl Found
50	222–223	*b,p*	A	$C_{20}H_{28}N_4 \cdot 2H_2SO_4 \cdot 1.5H_2O$[uu]	9.80	9.78	...	...
51	257–258	*e,p*	A	$C_{20}H_{28}N_4 \cdot 2H_2SO_4$[ww]	10.76	10.79	...	...

[a] These compounds are mixtures of *cis* and *trans* isomers unless otherwise indicated. They were prepared by method A or B, the reduction of the diamides of Tables III or IV, as indicated. A few of the compounds were prepared by other methods as indicated by footnotes. [b] Methanol. [c] Prepared from the commercially available free base. [d] This compound is a 1,4-*trans* isomer. [e] Ethanol. [f] This compound is a mixture of the 6- and 7-octenyl derivatives. [g] Prepared by catalytic hydrogenation of **8** in glacial acetic acid with platinum oxide at atmospheric pressure and room temperature. [h] C_6H_{11} ≡ cyclohexyl. [i] This compound is a 1,4-*cis* isomer. [j] C_4H_7 ≡ cyclobutyl. [k] Acetonitrile. [l] C_5H_9 ≡ cyclopentyl. [m] Ether. [n] Prepared by hydrogenation of **51** with platinum oxide in ethanol at room temperature and atmospheric pressure. [o] Calcd.: C, 69.3; H, 10.30. Found: C, 69.10; H, 10.01. [p] Water. [q] Acetone. [r] Good analyses could not be obtained for these two compounds. Thin layer chromatography and infrared spectra indicate that they exist in equilibrium with their free bases even when the salts are prepared under forcing conditions. [s] 2-Propanol. [t] C_7H_{13} ≡ cycloheptyl. [u] C_8H_{15} ≡ cyclooctyl. [v] Calcd.: C, 69.66; H, 11.28. Found: C, 69.79; H, 11.47. [w] Calcd.: C, 68.68; H, 11.08. Found: C, 68.76; H, 10.58. [x] Calcd.: C, 71.40; H, 11.98. Found: C, 71.42; H, 11.87. [y] A low-melting ether-soluble isomer. [z] Ethyl acetate. [aa] Calcd.: C, 70.98; H, 11.31. Found: C, 71.12; H, 11.04. [bb] A high-melting ether-insoluble isomer. [cc] Calcd. C, 70.98; H, 11.31. Found: C, 71.11; H, 11.46. [dd] C_4H_8N ≡ pyrrolidino. [ee] $C_5H_{10}N$ ≡ piperidino. [ff] Calcd. C, 61.54; H, 10.33. Found: C, 61.68; H, 10.10. [gg] $C_6H_{12}N$ ≡ hexamethyleneimino. [hh] Prepared by the Eschweiler–Clarke modification of the Leuckart reaction on **1**, Table I. [ii] $C_9H_{10}N$ ≡ 1,2,3,4-tetrahydroisoquinolino. [jj] Calcd.: Br, 29.80. Found: Br, 29.27. [kk] Prepared by the action of ethyl chloroformate on **4**, Table I. [ll] C_9H_9 ≡ 1-indanyl. [mm] C_9H_9 ≡ 2-indanyl. [nn] Calcd.: C, 83.37; H, 9.15. Found: C, 83.16; H, 8.95. [oo] Prepared by the alkylation of cyclohexane-1,4-bis(methylamine) with phenethylchloride in refluxing benzene. The free base had b.p. 224° (0.4 mm.). [pp] $C_{10}H_7$ ≡ 1-naphthyl. [qq] $C_{10}H_7$ ≡ 2-naphthyl. [rr] C_4H_3O ≡ 2-furyl. [ss] C_4H_3S ≡ 2-thienyl. [tt] C_5H_4N ≡ 2-pyridyl. [uu] Calcd.: S, 11.65; H_2O, 4.9. Found: S, 11.13; H_2O, 4.9. [vv] C_5H_4N ≡ 4-pyridyl. [ww] Calcd.: S, 12.31. Found: S, 11.65.

TABLE III

N,N′-DIACYL DERIVATIVES OF CYCLOHEXANE-1,4-BIS(METHYLAMINE)[a]



No.	R_1	R_2	M.p., °C.	Recrystn. Solvent	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found
1	H[b]	H	186–188	*c*	$C_{10}H_{18}N_2O_2$[d]	...	...	...	...
2	CH_3	H	203–230[e]	*f*	$C_{12}H_{22}N_2O_2$[g]	...	...	...	...
3	$(CH_2)_2CH_3$[h]	H	208–209	*c*	$C_{16}H_{30}N_2O_2$	68.05	67.94	10.71	10.70
4	$(CH_2)_5CH_3$[h]	H	194–195	*i,j*	$C_{22}H_{42}N_2O_2$	72.08	72.44	11.55	11.21
5	C_6H_{11}[k,h]	H	288–289	*c*	$C_{22}H_{38}N_2O_2$	72.88	72.33	10.56	10.43
6	C_6H_{11}[k,l]	H	214–215	*c*	$C_{22}H_{38}N_2O_2$[m]	72.88	73.11	10.56	10.42
7	C_4H_7[n,h]	H	246–247	*c*	$C_{18}H_{30}N_2O_2$	70.55	69.64	9.87	9.33
8	C_5H_9[o,h]	H	264–265	*c*	$C_{20}H_{34}N_2O_2$	71.81	71.57	10.24	10.98
9		H	197–200	*c*	$C_{22}H_{34}N_2O_2$	73.69	73.41	9.56	9.72
10	$-CH_2C_6H_{11}$[k,h]	H	276–278	*c,i*	$C_{24}H_{42}N_2O_2$	73.19	73.47	10.84	10.52
11	$-(CH_2)_2C_6H_{11}$[k]	H	220–221	*c*	$C_{26}H_{46}N_2O_2$	74.59	74.29	11.08	10.55
12	$2\text{-}CH_3SC_6H_5$	H	172–173	*i,j*	$C_{24}H_{30}N_2O_2S_2$[p]	...	...	...	...
13	$(CH_2)_2CH_3$[h]	C_7H_6Cl[q]	146–148	*r*	$C_{30}H_{40}Cl_2N_2O_2$[s]	...	...	...	...

[a] These compounds are mixtures of *cis* and *trans* isomers unless otherwise indicated; they were prepared by method C unless indicated to the contrary. [b] This diformyl derivative was prepared from formic acid and cyclohexane-1,4-bis(methylamine) (see Experimental). [c] Methanol. [d] Calcd.: N, 14.14. Found: N, 14.21. [e] The corresponding 1,4-*trans* isomer is reported to have m.p. 230° [R. Malachowski, J. Wasowska, and S. Jozkiewicz, *Ber.*, **71**, 759 (1938)]. [f] Ethyl acetate. [g] Calcd.: N, 12.38. Found: N, 12.33. [h] This compound is a 1,4-*trans* isomer. [i] Water. [j] Ethanol. [k] C_6H_{11} ≡ cyclohexyl. [l] This compound is a 1,4-*cis* isomer. [m] Calcd.: N, 7.73. Found: N, 7.63. [n] C_4H_7 ≡ cyclobutyl. [o] C_5H_9 ≡ cyclopentyl. [p] Calcd.: N, 6.33; S, 14.49. Found: N, 6.11; S, 14.32. [q] C_7H_6Cl ≡ 2-chlorobenzyl. [r] Dioxane. [s] Calcd.: Cl, 13.34; N, 5.27. Found: Cl, 13.12; N, 5.26.

and sodium hydroxide (12.0 g., 0.3 mole) at 0°. The solid amide was isolated by filtration and was crystallized from methanol to yield pure material, 19.5 g. (69%).

The acid chlorides used in the preparation of the diamides of Table III were obtained from the corresponding acids with thionyl chloride. The acids, or in some cases the acid chlorides, were commercially available except for the following: cyclohexylacetic acid and β-cyclohexylpropionic acid, prepared by catalytic hydrogenation of the corresponding aromatic acid; 1-cyclohexenecarboxylic acid[7] and 2-methylmercaptobenzoyl chloride.[8]

N,N′-Diformylcyclohexane-1,4-bis(methylamine) (**Table III, 1**).—Cyclohexane-1,4-bis(methylamine) (28.4 g., 0.2 mole) and 90% formic acid (25.6 g., 0.5 mole) were refluxed for 22 hr. in toluene (200 ml.) and the theoretical volume of water was collected in a Dean–Stark trap. The product was insoluble in toluene and was isolated by decantation of the solvent. Crystallization from methanol yielded pure material (30%).

Method D. N,N′-Hexamethylenecyclohexane-*trans*-1,4-dicarboxamide (**Table IV, 9**).—Cyclohexane-*trans*-1,4-dicarboxyl chloride[9] (10.0 g., 0.05 mole) dissolved in benzene (30 ml.) was added dropwise to hexamethyleneimine (19.8 g., 0.2 mole) in benzene (200 ml.) and the mixture refluxed for 5 hr. The precipitate was removed by filtration and the filtrate was evapo-

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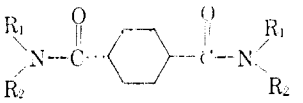
(9) R. Malachowski, J. J. Wasowska, S. Jozkiewiez, J. Adamiczka, and G. Zinnmerman-Pasternak, *Ber.*, **71**, 759 (1958).

TABLE IV

N,N'-POLYSUBSTITUTED DERIVATIVES OF *trans*-CYCLOHEXANE-1,4-DICARBOXAMIDE[a]



No.	R_1, R_2	M.p., °C.	Recrystn. solvent	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found
1	NHCH– 	302–307	*b,c*	$C_{34}H_{34}N_2O_2$[d]	75.35	75.37	8.96	9.08
2	NHCH– 	240–245	*b,e*	$C_{30}H_{34}N_2O_4$	65.54	65.40	9.35	9.31
3	$NHC(CH_3)_3$	>310	*b,e*	$C_{16}H_{30}N_2O_2$	68.05	68.29	10.71	10.73
4	$NHC(CH_3)_2CH_2C(CH_3)_3$	231–233	*b,e*	$C_{24}H_{46}N_2O_2$	73.05	73.35	11.75	11.81
5	NHC_6H_{11}[f]	>360	*g*	$C_{30}H_{34}N_2O_2$[h]	71.81	71.45	10.25	9.99
6	NHC_7H_{13}[i]	>360	*g*	$C_{32}H_{38}N_2O_2$[j]	...	...	...	...
7	C_4H_8N[k]	253–255	*l*	$C_{16}H_{26}N_2O_2$[m]	69.03	69.23	9.41	9.48
8	$C_5H_{10}N$[n]	188–189	*e*	$C_{18}H_{30}N_2O_2$[o]	70.55	70.70	9.87	9.82
9	$C_6H_{12}N$[p]	183–184	*e*	$C_{20}H_{34}N_2O_2$	71.81	71.48	10.25	9.83
10	$C_9H_{10}N$[q]	244–245	*l*	$C_{26}H_{30}N_2O_2$[r]	77.58	77.24	7.51	7.53
11	NHC_9H_9[s]	>310	*c*	$C_{26}H_{30}N_2O_2$[t]	77.58	77.62	7.51	7.52
12	NHC_9H_9[u]	>310	*v*	$C_{26}H_{30}N_2O_2$	77.58	77.37	7.51	7.63

[a] These compounds were prepared by method D (see Experimental). [b] Water. [c] Ethanol. [d] Calcd.: N, 7.32. Found: N, 7.49. [e] Methanol. [f] C_6H_{11} ≡ cyclohexyl. [g] Dimethylformamide. [h] Calcd.: N, 8.38. Found: N, 8.32. [i] C_7H_{13} ≡ cycloheptyl. [j] Calcd.: N, 7.73. Found: N, 8.15. [k] C_4H_8N ≡ pyrrolidino. [l] Chloroform. [m] Calcd.: N, 10.07. Found: N, 9.96. [n] $C_5H_{10}N$ ≡ piperidino. [o] Calcd.: N, 9.14. Found: N, 9.35. [p] $C_6H_{12}N$ ≡ hexamethyleneimino. [q] $C_9H_{10}N$ ≡ 1,2,3,4-tetrahydroisoquinolino. [r] Calcd.: N, 6.96. Found: N, 6.77. [s] C_9H_9 ≡ 1-indanyl. [t] Calcd.: N, 6.96. Found: N, 7.04. [u] C_9H_9 ≡ 2-indanyl. [v] Analytical sample sublimed at 280° (0.01 mm.).

rated *in vacuo* to yield a solid residue (20 g.). Crystallization from methanol yielded pure material.

In some cases the diamides were insoluble in benzene and these were isolated by evaporating the reaction mixture to dryness and removing amine hydrochloride by trituration with water. All the required amines were commercially available except 2-indanylamine which was prepared as described by Levin, *et al.*[10]

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(10) N. Levin, B. E. Graham, and H. G. Kolloff, *J. Org. Chem.*, **9**, 380 (1944).

Synthesis of 3,5,3′,5′-Halogen-Substituted Thyropropionic Acids[1]

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In the course of an investigation of the reaction of 4-hydroxy-3,5-diiodophenylpyruvic acid with analogs of 3,5-diiodotyrosine in the presence of oxygen to form analogs of thyroxine,[3] it became necessary to synthesize various 3,5,3′,5′-tetrahalogenothyropropionic acids (see Table I). The synthesis of these compounds has been carried out according to the standard method using di-*p*-anisyliodonium bromide,[4] followed by halogenation of 3,5-dihalogenothyropropionic acids obtained.

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(3) A. Nishinaga and T. Matsuura, *J. Org. Chem.*, **29**, 1812 (1964).

Experimental[5]

Methyl 3-(4-Hydroxy-3,5-dihalogenophenyl)propionates.—These esters were prepared by Fischer's esterification of the corresponding acids[3,6,7]; diiodo ester, m.p. 74–75°; dibromo ester, m.p. 54–55°; dichloro ester, m.p. 70–72°.

General Procedure for the Preparation of 3,5-Dihalogenothyropropionic Acids (I, X_1 = H; X_2 = Halogen).—A slight modification of the procedure of Ziegler and Maar[4] was used for the preparation of these acids. A mixture of di-*p*-anisyliodonium bromide[4] (8 mmoles), methyl 3-(4-hydroxy-3,5-dihalogenophenyl)propionate (4 mmoles), triethylamine (4 mmoles), and copper powder (8 mg.-atoms) in 4 ml. of methanol was stirred at room temperature for several hours, then allowed to stand overnight. The copper powder was removed by filtration and washed with methanol. The filtrate and washing were combined and evaporated under reduced pressure. The residue was taken up in 50 ml. of benzene and the benzene solution was washed with 1 *N* HCl, water, 1 *N* NaOH, water, and 5% aqueous acetic acid, then evaporated. The residue was subjected to steam distillation until no more *p*-iodoanisol distilled. The water was then decanted and the residue was refluxed for 2 hr. in a mixture of 8 ml. of acetic acid and 8 ml. of concentrated HBr. In the preparation of I (X_1 = H; X_2 = I), hydriodic acid (*d* 1.7) was used in place of HBr. The reaction mixture was concentrated under reduced pressure and diluted with water to yield crystals of I.

Bromination of I (X_1 = Br or I).—The bromination was carried out in an acetic acid solution with an excess of bromine. After standing at room temperature for a few days, the reaction mixture was worked up as usual.

Iodination of I (X_1 = H; X_2 = Cl or Br).—The iodination was carried out in an aqueous methylamine solution according to the procedure of Kharasch, *et al.*[8]

(4) H. Ziegler and C. Maar, *ibid.*, **27**, 3335 (1962); see also G. Hillemann, *Z. Naturforsch.*, **11b**, 419 (1956); P. E. Bevilacqua, J. T. Plati, and W. Wenner, U. S. Patent 2,895,927 (July 21, 1959).

(5) Melting points were determined in capillary tubes. The microanalyses were made by Mr. J. Goda and his associates, of this faculty.

(6) J. H. Barnes, E. T. Borrows, J. Elks, B. A. Heus, and A. G. Long, *J. Chem. Soc.*, 2824 (1950).

(7) T. Matsuura and H. J. Calnmann, *J. Am. Chem. Soc.*, **82**, 2055 (1960).

(8) N. Kharasch, S. H. Kalfayan, and J. D. Arterberry, *J. Org. Chem.*, **21**, 925 (1956).