[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ILLINOIS]

CYCLOHEXYL AND CYCLOHEXYLMETHYL ALKYL ACETIC ACIDS AND THEIR ACTION TOWARD B. LEPRAE. X[1]

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In a previous paper, the preparation of three series of acids was described, β-cyclohexylethyl, γ-cyclohexylpropyl and δ-cyclohexylbutyl alkyl acetic acids. Of these acids those containing from 16 to 18 carbon atoms were found to have an especially high bactericidal action toward *B. Leprae* and a distinctly greater effect than the isomeric acids with the carboxyl group at the end of the side chain.

In this investigation the two series, cyclohexyl (I) and cyclohexylmethyl (II) alkyl acetic acids were made and tested, where the R in (I)

$$\underset{\text{I}}{C_6H_{11}CH(CO_2H)R} \qquad \underset{\text{II}}{C_6H_{11}CH_2CH(CO_2H)R}$$

represents alkyl groups varying in size from ethyl to lauryl and the R in (II) from ethyl to *n*-octyl. In these series, also, the most effective acids were those containing 16 to 18 carbon atoms, as may be seen in Table I.

TABLE I

BACTERIOLOGICAL TESTS TO *B. Leprae*

	Dilutions of sodium salts in thousand																										
	10	20	30	40	50	60	70	80	90	100	110	120	130	140	150	160	170	180	190	200	220	240	260	280	300	320	340
Cyclohexyl alkyl acetic acids, $C_6H_{11}CH(CO_2H)R$. R =																											
n-C_5H_{11}	−	−	+	+	+	+	+	+	+	+					+					+							
n-C_6H_{13}	−	−	−	−	±	+	+	+	+	+					+					+							
n-C_7H_{15}	−	−	−	−	−	−	−	−	−	−	±	+	+	±	+	+	+	+	+	+			+		+		
n-C_8H_{17}	−	−	−	−	−	−	−	−	−	−	−	+	+	±	±	−	+	+	+	+			+		+		
n-C_9H_{19}	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	±	+	−	+		
n-$C_{10}H_{21}$										−	−	−	−	−	−	−	−	−	±	±			+		+		
n-$C_{11}H_{23}$										−	−	−	−	−	−	−	±	−	−	±			+		+		
n-$C_{12}H_{25}$	−	−	−	−	−	−	±	±	±	±	±	±	+	+	+	±	+	−	+								
Cyclohexylmethyl alkyl acetic acids, $C_6H_{11}CH_2CH(CO_2H)R$. R =																											
C_2H_5	−	−	+	+	+	+	+	+	+	+																	
n-C_3H_7	+	+	+	+	+	+	+	+	+	+																	
n-C_4H_9	−	+	+	+	+	+	+	+	+	+																	
n-C_5H_{11}	−	−	−	−	−	±	+	+	+	+																	
n-C_6H_{13}	−	−	−	±	+	±	±	±	+	+																	
n-C_7H_{15}	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	±	+	+	+	±	−	±	±
n-C_8H_{17}	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	±	−	±	+	−	−	±	±

[1] Previous papers in this field are: (a) Shriner and Adams, THIS JOURNAL, **47**, 2727 (1925); (b) Noller with Adams, *ibid.*, **48**; 1074 (1926); (c) **48**, 1080 (1926); (d) Hiers with Adams, *ibid.*, **48**, 1089 (1926); (e) Van Dyke and Adams, *ibid.*, **48**, 2393 (1926); (f) Sacks with Adams, *ibid.*, **48**, 2395 (1926); (g) Hiers with Adams, *ibid.*, **48**, 2385 (1926); (h) Adams, Stanley, Ford and Peterson, *ibid.*, **49**, 2934 (1927); (i) Arvin and Adams, *ibid.*, **49**, 2940 (1927).

[2] This communication is an abstract of portions of theses presented by W. M. Stanley and H. A. Stearns in partial fulfilment of the requirements for the Degree of Doctor of Philosophy, in Chemistry, at the University of Illinois.

As in the first three series studied a certain molecular weight appears to be necessary before bactericidal action is found and it then increases with molecular weight until a maximum figure is reached.

In order to have a direct comparison of isomeric acids in these cyclohexyl series, where the carboxyl is on the first, second, third, fourth and fifth carbon atoms, respectively, from the ring, Table II has been arranged selecting, however, merely the most bactericidal acids.[1h] The dilutions of the sodium salts, which represent the maximum values that will kill with certainty, are listed for each isomer.

TABLE II

COMPARISON OF BACTERICIDAL VALUE OF CERTAIN ISOMERS OF FIVE CYCLOHEXYL SERIES

	R =	Maximum dilution of sodium salts in thousands
$C_6H_{11}CH(CO_2H)R$	C_8H_{17}	110
	C_9H_{19}	190
	$C_{10}H_{21}$	180
$C_6H_{11}CH_2CH(CO_2H)R$	C_7H_{15}	190
	C_8H_{17}	190
	C_9H_{19}	...
$C_6H_{11}(CH_2)_2CH(CO_2H)R$	C_6H_{13}	160
	C_7H_{15}	220
	C_8H_{17}	320
$C_6H_{11}(CH_2)_3CH(CO_2H)R$	C_5H_{11}	170
	C_6H_{15}	240
	C_7H_{15}	220
$C_6H_{11}(CH_2)_4CH(CO_2H)R$	C_4H_9	190
	C_5H_{11}	220
	C_6H_{13}	180

It is obvious that the location of the carboxyl group on the chain has comparatively little effect. Although the acids of the cyclohexylethyl and cyclohexylpropyl series appear to kill in somewhat higher dilutions than the isomers in the other series, it may be stated that the errors in bacteriological work are large, and much more evidence should be available before there would be safety in such a conclusion.

The acids of Series I were prepared by condensing the proper alkyl halides with cyclohexyl malonic ester and saponifying. The acids of Series II were made also by saponification of the corresponding malonic esters. Cyclohexylmagnesium bromide and formaldehyde gave cyclohexylcarbinol, which in turn was converted to the bromide[1g] and condensed with malonic ester. The alkyl groups of varying sizes were then introduced.

Experimental

Alkyl Halides.—Most of these were prepared as described in a previous paper.[1h] Those used in this investigation which have not been employed before were *n*-decyl bromide, *n*-undecyl bromide and lauryl bromide. They were all made from the corresponding alcohols with hydrobromic acid and sulfuric acid, and all but the first will be described in more detail in the following paper.

Substituted Malonic Esters.—These were prepared as previously described. Cyclohexyl malonic ester and cyclohexylmethyl malonic ester were condensed with alkyl bromides. Part of the condensations were carried out as in the earlier investigations and part in an inert solvent. The latter seemed to give better yields.

Substituted Malonic Acids.—A slight modification of the procedure used previously proved advantageous. The disubstituted malonic esters were shaken with an excess of hot, saturated alcoholic potassium hydroxide solution and then refluxed overnight. The condenser was removed and the alcohol allowed to evaporate. The last traces of alcohol were then removed by heating under diminished pressure for two or three hours to 120° in an oil-bath. The solid potassium salt was dissolved in a little water and a small amount of ether added, the latter to take care of any unsaponified ester. The mixture was poured into a separatory funnel and the aqueous solution of potassium salt drawn off and run into an excess of ice and hydrochloric acid. During this neutralization the mixture should be shaken or stirred well and also for several minutes afterwards. The free malonic acid was extracted with ether. This may be purified from benzene or acetone, or in a crude state converted directly

TABLE III

DIETHYL CYCLOHEXYL ALKYL MALONATES. $C_6H_{11}C(CO_2C_2H_5)_2R$

R =	B. p., °C. (2 mm.)	n_D^{25}	d_4^{25}	Calcd., % C	Calcd., % H	Found, % C	Found, % H
n-C_5H_{11}	121–125	1.4553	0.9850	69.17	10.33	69.31	10.26
n-C_6H_{13}	126–130	1.4559	.9755	69.88	10.50	70.28	10.65
n-C_7H_{15}	135–139	1.4562	.9685	70.52	10.66	70.41	10.75
n-C_8H_{17}	144–148	1.4564	.9638	71.12	10.81	71.45	10.79
n-C_9H_{19}	149–154	1.4567	.9574	71.67	10.94	71.66	10.85
n-$C_{10}H_{21}$	157–161	1.4570	.9540	72.19	11.07	72.58	10.87
n-$C_{11}H_{23}$	170–175	1.4574	.9532	72.66	11.18	72.31	11.12
n-$C_{12}H_{25}$	185–189	1.4589	.9466	73.14	11.29	72.63	11.22

TABLE IV

DIETHYL CYCLOHEXYLMETHYL ALKYL MALONATES. $C_6H_{11}CH_2C(CO_2C_2H_5)_2R$

R =	B. p., °C.	n_D^{20}	d_4^{20}	Calcd., % C	Calcd., % H	Found, % C	Found, % H
C_2H_5	143–145 (4.5 mm.)	1.4542	1.0104	67.55	9.92	67.75	10.02
n-C_3H_7	154–155 (3 mm.)	1.4529	1.0062	68.41	10.13	67.69	10.11
n-C_4H_9	157–159 (4.5 mm.)	1.4548	0.9910	69.18	10.33	69.07	10.19
n-C_5H_{11}	159–160 (4 mm.)	1.4558	.9853	69.89	10.50	69.57	10.52
n-C_6H_{13}	160–163 (2.5 mm.)	1.4544	.9721	70.53	10.66	70.66	10.89
n-C_7H_{15}	183–185 (5 mm.)	1.4560	.9679	71.13	10.88	71.76	11.02
n-C_8H_{17}	178–181 (3 mm.)	1.4570	.9612	71.68	10.94	71.28	10.91

to the monobasic acid. Since many of the malonic acids had properties which rendered them difficult to purify completely, most of them were converted directly to the monobasic acids.

Monobasic Acids.—These acids were prepared by heating the malonic acid for several hours under reflux to 20–30° above their melting points.

TABLE V

CYCLOHEXYLMETHYL ALKYL MALONIC ACIDS. $C_6H_{11}CH_2C(CO_2H)_2R$

R =	M. p., °C.	Calcd., % C	Calcd., % H	Found, % C	Found, % H
C_2H_5	127.5–130	63.12	8.83	62.94	8.91
n-C_3H_7	145–147	64.71	9.15	64.76	9.03
n-C_4H_9	132–134	65.59	9.44	65.95	9.49
n-C_5H_{11}	132–135	66.62	9.70	66.37	9.56

TABLE VI

CYCLOHEXYL ALKYL ACETIC ACIDS. $C_6H_{11}CH(CO_2H)R$

R =	B. p., °C.	n_D^{25}	d_4^{25}	Calcd., % C	Calcd., % H	Found, % C	Found, % H
n-C_5H_{11}	136–139 (3 mm.)	1.4640	0.9544	73.51	11.40	73.31	11.25
n-C_6H_{13}	145–149 (3 mm.)	1.4641	.9449	74.27	11.58	74.44	11.45
n-C_7H_{15}	148–152 (2 mm.)	1.4641	.9350	74.92	11.75	74.74	11.66
n-C_8H_{17}	158–161 (2 mm.)	1.4642	.9298	75.52	11.89	75.88	11.97
n-C_9H_{19}	167–171 (3 mm.)	1.4645	.9245	76.04	12.02	75.56	11.66
n-$C_{10}H_{21}$	165–169 (2 mm.)	1.4649	.9224	76.51	12.14	76.98	11.91
n-$C_{11}H_{23}$	173–177 (2 mm.)	1.4650	.9166	76.95	12.25	76.72	12.01
n-$C_{12}H_{25}$	187–191 (2 mm.)	1.4653	.9129	77.34	12.34	76.91	12.27

TABLE VII

CYCLOHEXYLMETHYL ALKYL ACETIC ACIDS. $C_6H_{11}CH_2CH(CO_2H)R$

R =	B. p., °C.	n_D^{25}	d_4^{25}	Calcd., % C	Calcd., % H	Found, % C	Found, % H
C_2H_5	131–132 (2 mm.)	1.4623	0.9814	71.68	10.94	71.34	10.96
n-C_3H_7	141–143 (4.5 mm.)	1.4628	.9720	72.66	11.18	72.10	10.93
n-C_4H_9	133–136 (3 mm.)	1.4620	.9564	73.52	11.40	73.74	11.45
n-C_5H_{11}	139–142 (2 mm.)	1.4630	.9516	74.27	11.58	73.83	11.53
n-C_6H_{13}	174–175 (3 mm.)	1.4627	.9448	74.94	11.74	74.82	11.91
n-C_7H_{15}	202–204 (3 mm.)	1.4632	.9393	75.52	11.89	75.28	11.81
n-C_8H_{17}	186–190 (4 mm.)	1.4640	.9331	76.05	12.02	75.77	11.94

Summary

Two series of acids, cyclohexyl alkyl acetic acids and cyclohexylmethyl alkyl acetic acids have been prepared and their bactericidal effect toward *B. Leprae* determined. Those acids having 16 to 18 carbon atoms were especially effective.

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