amino ethers in alcohol have been recalculated. Some of the factors which determine the apparent change in relative base strength with change of solvent are discussed.

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CYCLOPROPYLMETHYL ALKYL ACETIC ACIDS AND THEIR BACTERICIDAL ACTION TOWARD B. LEPRAE. XIII[1]

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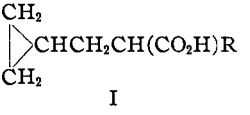
The various synthetic acids which have been studied for their bactericidal action have so far contained either a five or six membered ring. The present investigation has covered the synthesis of a series of acids containing a three-membered ring, namely, the cyclopropylmethyl alkyl acetic acids, (I) where the R varies from *n*-amyl to *n*-myristyl. These acids are of interest because they lead to the possibility of determining whether the significant factor for the bactericidal action in the many acids that have been studied is the character of the ring or is the molecular weight of the whole molecule, or merely that part of the molecule outside of the ring structure.



I

In Table I are given the bacteriological results.

TABLE I

CYCLOPROPYLMETHYL ALKYL ACETIC ACIDS, $C_3H_5CH_2CH(CO_2H)R$

	Dilutions of sodium salt in thousands																			
R =	10	20	30	40	50	60	70	80	90	100	111	125	133	143	153	167	176	185	200
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-$C_{12}H_{25}$										−	−	±	−	+	+	+	+	+	+
n-$C_{14}H_{29}$										+	+	+	+	+	+	+	+	+	+

It is noticeable that practically no bactericidal effect appears until the R group is *n*-octyl or larger. The two most effective acids were those containing the decyl and the undecyl groups. It appears, then, that in this as in other series, at least sixteen carbon atoms in the molecule must

[1] Paper XII in this series, THIS JOURNAL, **50**, 1790 (1928).

[2] This communication is an abstract of a portion of a thesis submitted by J. A. Arvin in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry at the University of Illinois.

be present before the bactericidal effect approaches the maximum. In Table II are the most effective acids of four series.

TABLE II

COMPARISON OF BACTERIOLOGICAL RESULTS OF VARIOUS COMPOUNDS

General formula R'CH(CO$_2$H)R	R=	R$_1$	Max. effective dil. in thousands	Empirical formula
$C_3H_5CH_2CH(CO_2H)R$	n-$C_{10}H_{21}$	C_4H_7	143	$C_{16}H_{30}O_2$
	n-$C_{11}H_{23}$	C_4H_7	153	$C_{17}H_{32}O_2$
$C_5H_9(CH_2)_2CH(CO_2H)R$	n-C_7H_{15}	C_7H_{13}	160	$C_{16}H_{30}O_2$
	n-C_8H_{17}	C_7H_{13}	170	$C_{17}H_{32}O_2$
$C_5H_9CH(CO_2H)R$	n-$C_{10}H_{21}$	C_5H_9	143	$C_{17}H_{32}O_2$
	n-$C_{11}H_{23}$	C_5H_9	153	$C_{18}H_{34}O_2$
$C_6H_{11}CH(CO_2H)R$	n-C_9H_{19}	C_6H_{11}	176	$C_{17}H_{32}O_2$
	n-$C_{10}H_{21}$	C_6H_{11}	176	$C_{18}H_{34}O_2$
$C_6H_{11}(CH_2)_2CH(CO_2H)R$	n-C_7H_{15}	C_8H_{15}	220	$C_{17}H_{32}O_2$
	n-C_8H_{17}	C_8H_{15}	320	$C_{18}H_{34}O_2$

It appears that there is no marked difference between the molecules containing different rings provided the molecular weight of the whole molecule is sufficiently large. It is interesting to note also that in those compounds of proper molecular weight, there seems to be a greater bactericidal effect where the two groups which are substituted in the acetic acid have approximately the same number of carbon atoms.

The acids were prepared by condensing cyclopropylmethyl bromide with malonic ester. The diethyl cyclopropylmethyl malonate was then condensed with the various alkyl bromides, the esters were saponified and carbon dioxide was eliminated.

Experimental

Cyclopropylmethyl Bromide.—This was made by the method of J. von Braun.[3] The last step in the procedure was not described in detail and was observed by the authors to require rather definite conditions if the best results were to be obtained.

In a 500-cc. Claisen flask, 135 g. of phosphorus tribromide was converted to pentabromide by the slow addition of 80 g. of bromine. The mixture was cooled during the addition and then allowed to stand for a few hours. The side arm of the Claisen flask was bent downward and extended through the neck well into the bulb of a 500-cc. distilling flask used as a receiver. The side arm of this receiving flask was also bent downward and connected in the same way to another distilling flask. The phosphorus pentabromide was heated in an oil-bath at 85–90° for a few minutes and then 79 g. of molten cyclopropylmethyl benzamide was added. When the contents of the flask were homogeneous, the system was evacuated and the receiving flasks were cooled by ice and salt mixtures. The reaction mixture was distilled until the temperature of the distilling vapors reached 150° at 18 mm. The distillate was poured into ice water and allowed to stand at 0–5° with occasional stirring for two hours. The product was separated, the aqueous layer extracted with a little ether and the whole washed with water. The crude material made in this way from three runs was fractionated and 87–91 g. (46–48%) of cyclopropylmethyl bromide was obtained; b. p. 104–110°.

[3] J. von Braun, *Ann.*, **445**, 201 (1925).

Diethyl Cyclopropylmethyl Malonate.—Cyclopropylmethyl bromide was condensed with malonic ester in the usual way, though the mixture was heated for forty hours before the reaction was complete. The yields were 66–70% of the theoretical.

Diethyl Cyclopropylmethyl Alkyl Malonates.—These were prepared by a method previously described, by the condensation of alkyl bromides with diethyl cyclopropylmethyl malonate.[4] The yields were 60–66% of the theoretical.

Cyclopropylmethyl Alkyl Acetic Acids.—These were prepared from the malonic acids by a method previously described.[4] The yields were 86–94% of the theoretical.

TABLE III

DIETHYL CYCLOPROPYLMETHYL ALKYL MALONATES, $C_3H_5CH_2C(CO_2C_2H_5)_2R$

R =	B. p., °C.	n_D^{20}	d_4^{20}	Calcd., % C	Calcd., % H	Found, % C	Found, % H
n-C_5H_{11}	122–125 (1.7 mm.)	1.4459	0.9770	67.56	9.93	67.02	9.73
n-C_6H_{13}	139–142 (2.9 mm.)	1.4470	.9685	68.40	10.14	67.98	10.08
n-C_7H_{15}	146–149 (2.7 mm.)	1.4481	.9613	69.17	10.33	68.71	10.22
n-C_8H_{17}	149–154 (2.3 mm.)	1.4491	.9559	69.88	10.50	69.70	10.41
n-C_9H_{19}	165–168 (2.5 mm.)	1.4503	.9512	70.53	10.67	70.73	10.76
n-$C_{10}H_{21}$	162–166 (1.9 mm.)	1.4510	.9460	71.13	10.81	70.93	10.80
n-$C_{11}H_{23}$	186–189 (3 mm.)	1.4519	.9419	71.68	10.95	71.52	10.85
n-$C_{12}H_{25}$	183–187 (2 mm.)	1.4526	.9395	72.19	11.07	71.71	10.97
n-$C_{14}H_{29}$	192–195 (1.9 mm.)	1.4530	.9377	73.11	11.29	73.37	11.01
H	129–133 (18 mm.)	1.4363	1.0216	61.61	8.58	61.03	8.32

TABLE IV

CYCLOPROPYLMETHYL ALKYL ACETIC ACIDS, $C_3H_5CH_2CH(CO_2H)R$

R =	M. p., °C.	B. p., °C.	n_D^{20}	d_4^{20}	Calcd., % C	Calcd., % H	Found, % C	Found, % H
n-C_5H_{11}	...	112–115 (1.4 mm.)	1.4469	0.9375	71.68	10.95	71.37	10.91
n-C_6H_{13}	...	130–132 (1.8 mm.)	1.4498	.9253	72.66	11.19	72.46	11.03
n-C_7H_{15}	...	136–139 (2 mm.)	1.4509	.9236	73.52	11.40	73.33	11.39
n-C_8H_{17}	...	146–149 (2.1 mm.)	1.4529	.9142	74.27	11.58	74.11	11.52
n-C_9H_{19}	...	162–164 (2.3 mm.)	1.4545	.9105	74.93	11.75	74.70	11.66
n-$C_{10}H_{21}$	...	176–178 (2.7 mm.)	1.4553	.9064	75.51	11.89	75.23	12.04
n-$C_{11}H_{23}$	27–28	186–189 (3 mm.)	....	....	76.05	12.03	75.72	11.93
n-$C_{12}H_{25}$	29–30	191–195 (3 mm.)	....	....	76.52	12.14	76.39	12.00
n-$C_{14}H_{29}$	35–37	176–179 (1.3 mm.)	....	....	77.34	12.39	76.76	12.19

Summary

A series of cyclopropylmethyl acetic acids has been prepared and tested for bactericidal action toward *B. Leprae*.

No appreciable bactericidal effect appeared until the alkyl group was *n*-octyl or larger, thus indicating as in previous researches that molecular weight of the whole molecule plays an important role. No marked difference was found between molecules containing 5-, 6- or 3-membered rings provided the molecular weight was approximately the same.

URBANA, ILLINOIS

[4] Adams, Stanley and Stearns, THIS JOURNAL, **50**, 1475 (1928).