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

Δ^2-CYCLOPENTENYLETHYL ALKYL ACETIC ACIDS AND THEIR BACTERICIDAL ACTION TOWARD B. LEPRAE. XII.[1]

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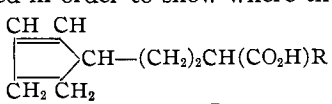
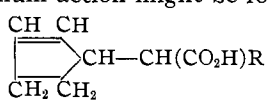
The fact that a Δ^2-cyclopentenyl group is present in chaulmoogric and hydnocarpic acids warrants a more extended investigation of synthetic acids containing this grouping than is described in an earlier paper. A complete series of Δ^2-cyclopentenylethyl alkyl acetic acids (I), where "R" varies from *n*-hexyl to *n*-lauryl, was prepared. This series was selected partly because of the comparative ease of preparation and partly because of the fact that it would probably be a more effective series than the Δ^2-cyclopentenyl alkyl acetic acids, judging from the greater effectiveness of cyclohexylethyl alkyl acetic acids over the cyclohexyl alkyl acetic acids.

A few members of the Δ^2-cyclopentenyl alkyl acetic series (II) where the "R" group is decyl, undecyl and lauryl were also made, since in the earlier investigation not a sufficient number of members of the series were prepared in order to show where the maximum action might be found.



I



II

In Tables I and II are given the bacteriological results on these compounds.

The most effective substances in Table I are those containing 16 to 19 carbon atoms in the molecule, as found for other acids previously described, and the degree of bactericidal action appears to be approximately the same as of those substances of essentially the same molecular weight found in other series.

TABLE I

Δ^2-CYCLOPENTENYLETHYL ALKYL ACETIC ACIDS, $C_5H_7(CH_2)_2CH(CO_2H)R$

	Dilutions of Sodium Salts in Thousands											
R =	25	36	50	62	74	85	100	125	147	165	192	230
C_6H_{13}	−	−	±	±	±	−	+	+	+	+	+	+
C_7H_{15}	−	−	−	−	−	−	±	−	−	−	±	+
C_8H_{17}	−	−	−	−	−	−	−	−	±	−	±	±
C_9H_{19}	−	−	−	−	−	−	−	−	−	±	−	+
$C_{10}H_{21}$	−	−	−	−	−	−	−	−	−	−	−	+
$C_{11}H_{23}$	−	−	−	−	−	±	±	±	+	+	+	+
$C_{12}H_{25}$	−	−	−	−	+	+	+	+	+	+	+	+

[1] Paper XI in this series, Yohe and Adams, THIS JOURNAL, 50, 1503 (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.

TABLE II

Δ^2-CYCLOPENTENYL ALKYL ACETIC ACIDS, $C_5H_7CH(CO_2H)R$

R =	Dilutions of Sodium in Thousands: 10	20	30	40	50	60	70	80	90	100	111	125	133	143	153	167	176	185	200
n-$C_{10}H_{21}$	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	±	+	+
n-$C_{11}H_{23}$	−	−	−	−	−	−	−	−	−	−	−	−	+	+	+	+	+	+	+
n-$C_{12}H_{25}$	−	−	−	−	−	−	−	−	−	±	−	±	±	+	+	+	+	+	+
X =	Δ^2-CYCLOPENTENYL ALKYL ACETIC ACIDS, $C_5H_7(CH_2)_xCO_2H$																		
3	±	±	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
5	−	±	±	±	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

In Table III the maximum bactericidal action obtained with the most effective isomers in series analogous to those prepared in this investigation is given.

TABLE III

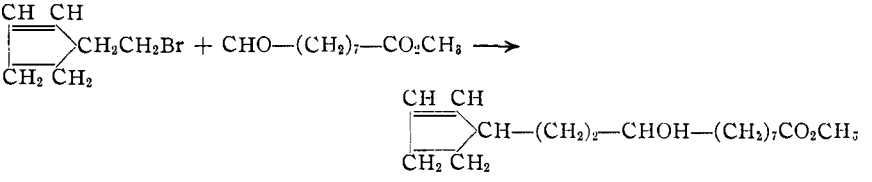
COMPARISON OF BACTERICIDAL EFFECT OF VARIOUS ANALOGS

	General Formula	R =	Max. effective dilution in thousands	Empirical formula
1.	$C_5H_7(CH_2)_2CH(CO_2H)R$ (cyclopentenyl)	n-C_7H_{15}	85	$C_{16}H_{28}O_2$
		n-C_8H_{17}	125	$C_{17}H_{30}O_2$
		n-C_9H_{19}	147	$C_{18}H_{32}O_2$
		n-$C_{10}H_{21}$	192	$C_{19}H_{34}O_2$
2.	$C_5H_7CH(CO_2H)R$ (cyclopentenyl)	n-C_9H_{19}	150	$C_{16}H_{28}O_2$
		n-$C_{10}H_{21}$	170	$C_{17}H_{30}O_2$
		n-$C_{11}H_{23}$	120	$C_{18}H_{32}O_2$
3.	$C_5H_9(CH_2)_2CH(CO_2H)R$ (cyclopentyl)	n-C_7H_{15}	160	$C_{16}H_{30}O_2$
		n-C_8H_{17}	170	$C_{17}H_{32}O_2$
4.	$C_5H_9CH(CO_2H)R$ (cyclopentyl)	n-C_9H_{19}	111	$C_{16}H_{30}O_2$
		n-$C_{10}H_{21}$	143	$C_{17}H_{32}O_2$
		n-$C_{11}H_{23}$	153	$C_{18}H_{34}O_2$
5.	$C_6H_{11}(CH_2)_2CH(CO_2H)R$ (cyclohexyl)	n-C_6H_{13}	160	$C_{16}H_{30}O_2$
		n-C_7H_{15}	220	$C_{17}H_{32}O_2$
		n-C_8H_{17}	320	$C_{18}H_{34}O_2$
6.	$C_6H_{11}CH(CO_2H)R$ (cyclohexyl)	n-C_8H_{17}	111	$C_{16}H_{30}O_2$
		n-C_9H_{19}	176	$C_{17}H_{32}O_2$
		n-$C_{10}H_{21}$	176	$C_{18}H_{34}O_2$
		n-$C_{11}H_{23}$	153	$C_{19}H_{36}O_2$

The differences between the bactericidal effects of compounds containing approximately the same number of carbon atoms is not significant enough to be worthy of discussion. It is of interest to note that by comparing series 1 and 2 with series 3 and 4 the olefin linkage has not produced any specific effect.

The chief raw material used for the preparation of these compounds was cyclopentenyl chloride, which has been described in previous articles. The cyclopentenylethyl bromide was prepared by the reduction of ethyl cyclopentenyl acetate, prepared in turn by the esterification of the acid produced by the malonic ester synthesis from cyclopentenyl chloride.

In earlier work an attempt was made by C. R. Noller to synthesize *d,l*-hydnocarpic acid by the condensation of Δ^2-cyclopentenylethyl magnesium bromide with methyl-8-aldehydo-octanoate and then elimination of the hydroxyl group. Before the work was entirely completed, the synthesis of *d,l*-chaulmoogric acid by Perkins through a different procedure led to the abandonment of the former research. Preparation of methyl-8-hydroxy-*d,l*-hydnocarpate and the corresponding acid had already been completed, so that the experimental results of Noller are described in this paper.



The bacteriological work was carried out by W. M. Stanley.

Experimental

Δ^2-Cyclopentenyl Ethanol.—This was prepared as described by Noller and Adams.[3]

Δ^2-Cyclopentenyl Ethyl Bromide.—A solution of 62.5 g. of cyclopentenyl ethanol in 150 cc. of dry toluene was cooled to $-5°$ and a solution of 50 g. of redistilled phosphorus tribromide in 100 cc. of toluene was added slowly with shaking at such a rate that the temperature did not rise above 0°. After the addition of the tribromide, the mixture was allowed to warm to room temperature, stand for one-half hour and was then heated on a steam-cone for one hour. The mixture was cooled, decomposed by pouring it into cold water, separated and the upper layer washed with a 5% solution of sodium hydroxide and then with water. The bromide thus obtained, after careful fractionation, boils at 71–72° at 16 mm. About 158 g. of bromide was obtained from 190 g. of alcohol; n_D^{20}, 1.4995; d_4^{20}, 1.2869.

Anal. Calcd. for $C_7H_{11}Br$: Br, 45.71. Found: 47.48.

Δ^2-Cyclopentenyl Butanol.—Δ^2-Cyclopentenyl ethyl magnesium bromide was condensed with ethylene oxide according to the procedure described by Hiers and Adams.[4] The average yield of the butanol was 38%; b. p. 118–123° at 24 mm.; n_D^{20}, 1.4723; d_4^{20}, 0.9317. Calcd. for $C_9H_{16}O$: C, 77.09, H, 11.52. Found: C, 76.91; H, 11.62.

As a by-product a substance boiling from 98–103° at 24 mm. was obtained, the structure of which was not determined.

Δ^2-Cyclopentenyl Butyl Bromide.—Δ^2-Cyclopentenyl butanol was converted to the bromide in a manner similar to the preparation of cyclopentenylethyl bromide from the corresponding alcohol. The product formed in 47% yields; b. p. 82–86° at 5 mm.; n_D^{20}, 1.4942; d_4^{20}, 1.2229.

Anal. Subs., 0.3370; 13.98 cc. of 0.1193 *N* $AgNO_3$. Calcd. for $C_9H_{15}Br$: Br, 39.35. Found: Br, 39.56.

Diethyl Δ^2-Cyclopentenyl Alkyl Malonates.—Diethyl Δ^2-cyclopentenylethyl and diethyl Δ^2-cyclopentenylbutyl malonates were prepared by the condensation of the corresponding bromides and malonic ester in the usual way; yields were about 66–69%.

[3] Noller with Adams, THIS JOURNAL, **48**, 2444 (1926).

[4] Hiers with Adams, *ibid.*, **48**, 2385 (1926).

Δ^2-Cyclopentenylalkyl Malonic Acids.—The malonic acids of this series were prepared according to the procedure described by Adams, Stanley and Stearns.[5] They were purified by recrystallization from benzene and were obtained in essentially quantitative yields.

Δ^2-Cyclopentenylethyl Acetic Acids and Δ^2-Cyclopentenylbutyl Acetic Acids.—These were prepared from the corresponding malonic acids by heating for a few hours at 150–155°.

Diethyl Δ^2-Cyclopentenyl and Diethyl Δ^2-Cyclopentenylethyl Alkyl Malonates.—

TABLE IV

DIETHYL Δ^2-CYCLOPENTENYLETHYL ALKYL MALONATES, $C_5H_7(CH_2)_2C(CO_2C_2H_5)_2R$

R =	B. p., °C.	n_D^{20}	d_4^{20}	Calcd., % C	Calcd., % H	Found, % C	Found, % H
n-C_6H_{13}	152–155 (2 mm.)	1.4598	0.9742	70.94	10.13	70.90	10.15
n-C_7H_{15}	159–162 (1.4 mm.)	1.4602	.9649	71.53	10.30	71.76	10.33
n-C_8H_{17}	178–181 (2 mm.)	1.4605	.9624	72.07	10.46	71.73	10.41
n-C_9H_{19}	176–180 (1.5 mm.)	1.4609	.9567	72.57	10.60	72.47	10.62
n-$C_{10}H_{21}$	183–187 (2.1 mm.)	1.4613	.9531	73.04	10.73	72.94	10.95
n-$C_{11}H_{23}$	190–194 (2.1 mm.)	1.4616	.9486	73.47	10.86	73.25	10.80
n-$C_{12}H_{25}$	197–201 (2.2 mm.)	1.4618	.9460	73.87	10.98	73.49	11.03
DIETHYL Δ^2-CYCLOPENTENYL ALKYL MALONATES, $C_5H_7C(CO_2C_2H_5)_2R$							
R =							
n-$C_{10}H_{21}$	170–172 (1.5 mm.)	1.4616	.9642	72.07	10.46	72.20	10.46
n-$C_{11}H_{23}$	176–180 (1 mm.)	1.4622	.9598	72.57	10.60	72.24	10.52
n-$C_{12}H_{25}$	193–196 (2 mm.)	1.4627	.9559	73.04	10.73	72.66	10.51
DIETHYL-ω-Δ^2-CYCLOPENTENYLALKYL MALONATES, $C_5H_7(CH_2)_xCH(CO_2C_2H_5)_2$							
X =							
4	152–155 (3 mm.)	1.4598	1.0077	68.04	9.29	67.71	9.57

TABLE V

Δ^2-CYCLOPENTENYLETHYL ALKYL ACETIC ACIDS, $C_5H_7(CH_2)_2CH(CO_2H)R$

R =	M. p., °C.	B. p., °C.	n_D^{20}	d_4^{20}	Calcd., % C	Calcd., % H	Found, % C	Found, % H
n-C_6H_{13}	.....	160–163 (2.3 mm.)	1.4697	0.9426	75.57	10.99	75.43	11.17
n-C_7H_{15}	.....	166–168 (2.2 mm.)	1.4698	.9358	76.12	11.19	76.37	11.14
n-C_8H_{17}	.....	174–176 (1.8 mm.)	1.4700	.9315	76.62	11.37	76.62	11.30
n-C_9H_{19}	.....	183–185 (2 mm.)	1.4701	.9269	77.06	11.51	76.88	11.56
n-$C_{10}H_{21}$	.....	186–188 (1.5 mm.)	1.4702	.9227	77.47	11.65	77.33	11.73
n-$C_{11}H_{23}$	.....	190–193 (1.3 mm.)	1.4703	.9196	77.84	11.77	77.68	11.76
n-$C_{12}H_{25}$	30–31.5	199–203 (1.5 mm.)			78.18	11.89	77.97	11.82
Δ^2-CYCLOPENTENYL ALKYL ACETIC ACIDS, $C_5H_7CH(CO_2H)R$								
R =								
n-$C_{10}H_{21}$	.....	183–186 (1.5 mm.)	1.4692	.9319	76.62	11.37	76.54	11.22
n-$C_{11}H_{23}$	36–38	188–190 (1.5 mm.)	....	...	77.06	11.51	76.72	11.39
n-$C_{12}H_{25}$	38–39	202–204 (2 mm.)	....	...	77.47	11.65	77.07	11.83
ω-Δ^2-CYCLOPENTENYLALKYL ACETIC ACIDS, $C_5H_7(CH_2)_xCO_2H$								
X =								
3		125–126 (4 mm.)	1.4718	.9904	70.14	9.16	70.16	9.52
5		149–154 (5 mm.)	1.4740	.9862	72.47	9.96	72.80	10.14

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

The diethyl Δ^2-cyclopentenyl alkyl malonates were prepared from diethyl Δ^2-cyclopentenyl malonate and the proper alkyl bromide by the procedure described by Adams, Stanley and Stearns.[5] The yields were 58–60%.

In a similar manner the Δ^2-cyclopentenylethyl bromide was condensed with diethyl alkyl malonates to give diethyl-Δ^2-cyclopentenylethyl alkyl malonates.

Δ^2-Cyclopentenyl Alkyl Acetic Acids and Δ^2-Cyclopentenylethyl Alkyl Acetic Acids.—The malonic esters were saponified with alcoholic potassium hydroxide as previously described and the potassium salt was obtained by evaporation to dryness. It was then dissolved in water and added to excess of concd. hydrochloric acid. Upon extraction with ether, evaporation of ether and heating for two hours at 160–165°, the monobasic acids were obtained. The yields were in the neighborhood of 90%.

Methyl-9-hydroxyhydnocarpate.—Δ^2-Cyclopentenylethyl bromide was converted into the corresponding Grignard in the usual way. This was then condensed with 8-aldehydo-octanoate in the proportion of 1 mole of aldehyde to 1 mole of Grignard reagent as shown by titration.[6] After working it up in the usual fashion, and after several careful fractional distillations, a constant boiling product was obtained; b. p. 177–179° at 2 mm.; n_D^{20}, 1.4720; d_4^{20}, 0.9874.

Anal. Calcd. for $C_{15}H_{30}O_3$: C, 71.91; H, 10.01. Found: C, 72.29; H, 10.70.

9-Hydroxy-*d,l*-Hydnocarpic Acid.—By saponification of the ester with alcoholic potassium hydroxide and working up in the manner described for the malonic acids, a solid acid was obtained which, upon crystallization from acetone, gave a constant m. p. of 62.0–62.8°.

Anal. Subs., 0.3688: 13.75 cc. of 0.1 *N* NaOH. Neut. equiv. Calcd. for $C_{14}H_{28}O_3$: 268.2. Found: 268.2.

Summary

1. A series of Δ^2-cyclopentenylethyl alkyl acetic acids has been prepared. Those members containing 16 to 18 carbon atoms showed a high bactericidal action toward *B. Leprae*.

2. Three of the higher members of the Δ^2-cyclopentenyl alkyl acetic acids have been prepared.

3. The synthesis of 9-hydroxy-*d,l*-hydnocarpic acid has been completed.

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[6] (a) Noller with Adams, THIS JOURNAL, **48**, 1074 (1926); (b) Davies and Adams, THIS JOURNAL, **50**, 1749 (1928).