HIGHER FATTY ACIDS

COMMUNICATION 3.* ALKYL-SUBSTITUTED GERANYLACETIC ACIDS

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For the purpose of studying the biological properties of substituted terpenylacetic acids and the relation of their properties of structure we synthesized some alkylgeranylacetic acids of general formula $(CH_3)_2C=CHCH_2CH_2C(CH_3)=CHCH_2CH(R)COOH$. The acids obtained have a bacteriostatic action toward M. tuberculosis. It is known that the bacteriostatic action of disubstituted acetic acids depends on their structure [2]. One of us has shown earlier that, as compared with analogous compounds containing substituents of normal structure, the presence of the geranyl group considerably intensifies the bacteriostatic effect [3], probably because of the high degree of branching of the molecule. Study of the acids synthesized showed that the degree of branching of the substituents in the series of alkyl-substituted geranylacetic acids also has an appreciable effect on the bacteriostatic activity [3]. Thus, the replacement of the primary n-hexyl group by the secondary 1-ethylbutyl group leads to an increase in the bacteriostatic effect by a factor of about 2.5 (the minimum concentrations of the sodium salt preventing the growth of M. tuberculosis were 45.4 γ/ml and 20.0 γ/ml respectively). In bacteriostatic action the hydrogenated substituted geranylacetic acids differ little from the corresponding unsaturated acids. Details of the biological study of substituted geranylacetic acids will be published separately.

The acids were synthesized by the alkylation of malonic ester, hydrolysis of the disubstituted malonic esters, isolation of the corresponding malonic acids, and their decarboxylation. The alkyl and the geranyl groups were introduced successively into malonic ester, or previously synthesized geranylmalonic ester was alkylated. The alkylation of unsubstituted malonic ester was conducted in absolute ethyl or butyl alcohol in presence of the corresponding alkoxide. To avoid the formation of heterogeneous products as a result of the transesterification of diethyl malonate, dibutyl malonate was used when the medium was butyl alcohol. It is known from the literature that monocarboxylic acids are often prepared from the corresponding disubstituted malonic esters, which are hydrolyzed with dilute aqueous-alcoholic or alcoholic solutions of potassium hydroxide [4-7]. Hydrolysis products are then formed which contain up to 65% of monoesters of the corresponding malonic acids.

The use of excess of a hot concentrated solution of potassium hydroxide for the hydrolysis of disubstituted malonic esters, by a slight modification of the method described by Adams and co-workers [8], gives quite satisfactory results, even in the hydrolysis of disubstituted malonic esters containing branched higher alkyl substituents. It is probable that under these conditions minimal amounts of monoesters are formed, for we were unable to isolate them either before decarboxylation or after decarboxylation in the form of monocarboxylic esters.

EXPERIMENTAL

The alkyl halides required were prepared by the reaction of the corresponding alcohols with dry hydrogen bromide in yields of 71-100% [9].

*For Communication 2 see [1].

TABLE 1. Substituted Geranylmalonic Esters $C_{10}H_{17}(R)C(COOC_2H_5)_2$

R	Molecular formula	B.p., °C (p, mm)	n_D^{20}	d_4^{20}	Found			Calculated			Yield, %	X in RX	Method
					MR	C, %	H, %	*MR*	C, %	H, %			
CH_3 [4]	$C_{18}H_{30}O_4$	152—158(5)	1,4640	0,9735	87,99	69,95	9,76	87,70	69,64	9,74	45,1	*	B
C_2H_5	$C_{19}H_{32}O_4$	140—142(1)	1,4653	0,9747	92,08	70,87	9,86	92,32	70,33	9,94	45,7	I	B
n C_3H_7	$C_{20}H_{34}O_4$	188—190(6)	1,4606	0,9532	96,86	70,65	10,06	96,93	70,97	10,12	53,1	I	B
C_3H_5	$C_{20}H_{32}O_4$	165—168(3)	1,4698	0,9744	96,31	70,81	9,94	95,47	71,39	9,59	70,0	Br	B
† *n*-C_4H_9 [12]	$C_{21}H_{36}O_4$	169,5—171(3,5)	1,4620	0,9503	101,98	71,48	10,27	101,55	71,55	10,29	63,4	Br	A
i-C_4H_9	$C_{21}H_{36}O_4$	147(2)	1,4624	0,9565	101,4	71,59	10,05	101,55	71,55	10,29	54,0	Br	A
sec-C_4H_9	$C_{21}H_{36}O_4$	179—182(3)	1,4674	0,9606	101,9	71,20	10,13	101,55	71,55	10,29	42,2	Br	A
n-C_5H_{11}	$C_{22}H_{38}O_4$	189—191(4)	1,4623	0,9469	106,48	71,72	10,30	106,17	72,09	10,45	31,0	Br	B
i-C_5H_{11}	$C_{22}H_{38}O_4$	165—168(1)	1,4642	0,9518	106,30	72,07	10,70	106,17	72,09	10,45	27,0	Cl	B
n-C_6H_{13} [13]	$C_{23}H_{40}O_4$	181—182(3)	1,4622	0,9425	111,05	72,82	10,50	110,79	72,59	10,59	56,0	Br	A
n-$C_3H_7(C_2H_5)CH$	$C_{23}H_{40}O_4$	175—176(2)	1,4678	0,9521	111,07	72,57	10,48	110,79	72,59	10,59	57,7	Br	A
n-C_8H_{17}	$C_{25}H_{44}O_4$	185—187(1)	1,4652	0,9392	120,32	73,77	10,40	120,02	73,48	10,85	41,2	Br	B
n-$C_6H_{13}(CH_3)CH$	$C_{25}H_{44}O_4$	192—194(2)	1,4646	0,9383	120,30	73,88	10,55	120,02	73,48	10,85	47,2	Br	A
n-$C_{15}H_{31}$	$C_{32}H_{58}O_4$	239,5—240(1)	1,4666	0,9206	152,64	75,54	11,31	152,35	75,84	11,54	43,4	Br	B
‡ C_2H_5	$C_{23}H_{42}O_4$	180—188(2)	1,4668	0,9416	112,70	73,11	10,45	112,99	72,59	10,59	48,3	I	B

*Dimethyl sulfate was used for the alkylation of the geranylmalonic ester.

†Prepared independently in 1948 by M. Asano and co-workers [12].

‡Dibutyl ethylgeranylmalonate.

TABLE 2. Substituted Geranylacetic $C_{10}H_{17}(R)CHCOOH$ and 2-Alkyl-5,9-dimethyldecanoic $C_{10}H_{21}(R)CHCOOH$ Acids

R	Molecular formula	B. p., °C (p, mm)	n_D^{20}	d_4^{20}	Found			Calculated			Yield, %
					MR	C, %	H, %	*MR*	C, %	H, %	
CH_3 [4]	$C_{13}H_{22}O_2$	163—168(3)	1,4715	0,9408	62,54	74,26	10,51	62,84	74,24	10,54	73,8
*C_2H_5	$C_{14}H_{24}O_2$	143,5—144(1)	1,4733	0,9308	67,65	75,21	10,77	67,45	74,95	10,78	75,0
n-C_3H_7	$C_{15}H_{26}O_2$	176—178(6)	1,4720	0,9232	72,30	75,47	11,10	72,07	75,58	10,99	72,3
C_3H_5	$C_{15}H_{24}O_2$	155—156(1)	1,4817	0,9376	71,83	76,27	10,03	71,60	76,23	10,24	67,3
† *n*-C_4H_9 [12]	$C_{16}H_{28}O_2$	166—168(3)	1,4720	0,9205	76,78	76,13	11,24	76,69	76,13	11,18	80,6
i-C_4H_9	$C_{16}H_{28}O_2$	148(1,5—2)	1,4697	0,9143	76,98	76,20	11,10	76,69	76,13	11,18	48,0
sec-C_4H_9	$C_{16}H_{28}O_2$	177—180(3)	1,4730	0,9268	76,40	76,37	11,30	76,69	76,13	11,18	80,6
n-C_5H_{11}	$C_{17}H_{30}O_2$	170,5—172(1)	1,4720	0,9143	81,60	76,68	11,28	81,31	76,64	11,35	72,0
i-C_5H_{11}	$C_{17}H_{30}O_2$	169—170(1)	1,4722	0,9143	81,61	76,67	11,50	81,31	76,64	11,35	80,0
n-C_6H_{13} [13]	$C_{18}H_{32}O_2$	168—171(3,5)	1,4708	0,9149	85,65	77,20	11,42	85,93	77,09	11,50	76,0
n-$C_3H_7(C_2H_5)CH$	$C_{18}H_{32}O_2$	179—182(5)	1,4740	0,9180	85,86	76,54	11,42	85,93	77,09	11,50	75,8
n-C_8H_{17}	$C_{20}H_{36}O_2$	192,5—193(1,5)	1,4713	0,9093	95,45	77,30	11,89	95,16	77,86	11,76	70,2
n-$C_6H_{13}(CH_3)CH$	$C_{20}H_{36}O_2$	202—206(3)	1,4754	0,9171	94,95	78,10	12,02	95,16	77,86	11,76	74,0
n-$C_{15}H_{31}$	$C_{27}H_{50}O_2$	247—250(1)	1,4740	0,8960	127,57	79,83	12,50	127,49	79,74	12,39	75,7
i-C_4H_9	$C_{16}H_{32}O_2$	155—157(10)	1,4462	0,8825	77,52	74,85	12,40	77,62	74,94	12,58	40,8
n-C_6H_{13}	$C_{18}H_{36}O_2$	205—208(12)	1,4486	0,8778	86,88	75,91	12,70	86,86	76,00	12,78	50,0
n-$C_3H_7(C_2H_5)CH$	$C_{18}H_{36}O_2$	163—165(2)	1,4506	0,8814	86,34	75,96	12,02	86,86	76,00	12,78	76,5

*From dibutyl ethylgeranylmalonate; yield 84.8%.

†Prepared in 1948 independently by M. Asano and co-workers [12].

Transesterification of Diethyl Malonate [10].* 0.6 g of sodium hydroxide was dissolved with heating in 1 liter of absolute butyl alcohol, 200 g of diethyl malonate was added, and the mixture was heated at the boil for three hours. The ethanol formed was distilled off, the butyl alcohol solution was washed with water, butyl alcohol was distilled off, and the residue was vacuum-fractionated. Dibutyl malonate, b. p. 102-105° (3 mm) and n_D^{20} 1.4280, was obtained in 80.5% yield. The literature [11] gives: b. p. 140° (18 mm), n_D^{20} 1.4264. If before the addition of diethyl malonate water was distilled from the solution of sodium hydroxide in butyl alcohol in the form of its azeotrope with butyl alcohol, the yield of dibutyl malonate is raised to 93-95%.

Dibutyl Geranylmalonate. One mole of dibutyl malonate was added to a solution of one mole of sodium butoxide prepared from sodium hydroxide and butyl alcohol with azeotropic distillation of water, and then one mole of geranyl bromide was added dropwise. The mixture was heated at the boil until the medium ceased to be alkaline. The precipitate formed was dissolved by the addition of water, the butyl alcohol layer was separated, butyl alcohol was distilled off under somewhat reduced pressure, and the residue was vacuum-fractionated. Dibutyl geranylmalonate, b. p. 168-171° (1 mm), n_D^{20} 1.4638; d_4^{20} 0.9598; was obtained in 30% yield. Found: C 71.28; H 10.74%; MR 101.31. $C_{21}H_{36}O_4F_2$. Calculated: C 71.55; H 10.29%; MR 101.55.

Preparation of Alkylgeranylmalonic Esters. Method A. One mole of alkylmalonic ester was added dropwise to a boiling suspension of 1 g-atom of sodium in 250-300 ml of toluene or xylene. The mixture was heated at the boil for 0.5-1.0 h, and then one mole of geranyl chloride or bromide was added to the boiling solution at such a rate that the mixture boiled gently. After the addition of the geranyl halide, the mixture was heated at the boil until no longer alkaline. The precipitate of salts was dissolved by the addition of water, the toluene or xylene layer was separated, solvent was driven off (water was removed simultaneously), and the residue was vacuum-fractionated. For purification the product was refractionated.

Method B. From one g-atom of sodium, one mole of geranylmalonic ester, and one mole of the alkyl halide, by heating the mixture in toluene or xylene until it was no longer alkaline, we obtained the alkylgeranylmalonic ester, which was purified by refractionation in a vacuum. The constants and yields of the alkylgeranylmalonic esters synthesized are given in Table 1.

Preparation of Alkylgeranylacetic Acids. The alkylgeranylmalonic ester was hydrolyzed with a boiling concentrated solution of potassium hydroxide in the ethanol-water azeotrope with vigorous stirring. To 100 g of the alkylgeranylmalonic ester we took 70 g of potassium hydroxide and 70-80 ml of alcohol. During the vigorous hydrolysis reaction the dipotassium alkylgeranylmalonate separated. To complete the hydrolysis the reaction mixture was heated for 0.5-2.0 h, and then alcohol was driven off as far as possible. The dipotassium salt was dissolved in water, and with stirring and cooling, dilute (1:1) hydrochloric acid was added to give an acid reaction (pH about 5), and the alkylgeranylmalonic acid liberated was extracted with xylene. To decarboxylate the alkylgeranylmalonic acid either the xylene extract was refluxed for 1-1.5 h, or xylene was distilled slowly from the extract at atmospheric pressure. After the removal of xylene the alkylgeranylacetic acid formed was purified by vacuum fractionation. The constants and yields of the alkylgeranylacetic acids obtained are given in Table 2.

Preparation of 2-Alkyl-5,9-dimethyldecanoic Acids. 0.03-0.05 mole of the alkylgeranylacetic acid was dissolved in 25-30 ml of the ethanol-water azeotrope and hydrogenated with hydrogen at atmospheric pressure in presence of 0.3 g of finely ground 5% Pt/C and a few drops of saturated palladium chloride solution with shaking in a hydrogenation flask. Hydrogenation was complete after a few hours. After the absorption of the theoretical amount of hydrogen, catalyst was filtered off, alcohol was distilled off, and the residue was refractionated in a vacuum. The hydrogenation product did not give qualitative reactions for a double bond. The constants and yields of the 2-alkyl-5,9-dimethyldecanoic acids obtained are given in Table 2.

SUMMARY

1. Twelve previously undescribed alkylgeranylacetic acids containing alkyl substituents with from 1 to 15 carbon atoms and thirteen corresponding alkylgeranylmalonic esters were synthesized and characterized. Three previously undescribed 2-alkyl-5,9-dimethyldecanoic acids were also prepared and characterized.

2. The previously undescribed dibutyl geranylmalonate and dibutyl ethylgeranylmalonate were synthesized and characterized.

*In the preparation of dibutyl malonate and dibutyl geranylmalonate diploma-holding student P. P. Rodionov of the Lomonosov Moscow Institute of Fine Chemical Technology took part.

3. Some data are given on the relation of the biological properties of disubstituted acetic acids to their structures: the bacteriostatic action of alkylgeranylacetic acids becomes more intense as the degree of branching of the alkyl substituent increases. The bacteriostatic action of alkyldimethyldecanoic acids is only slightly weaker than that of the corresponding unsaturated acids.

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