Derivatives of dl-Aminopropanediols*

By Chieko URAKAMI and Kasumi KAKEDA

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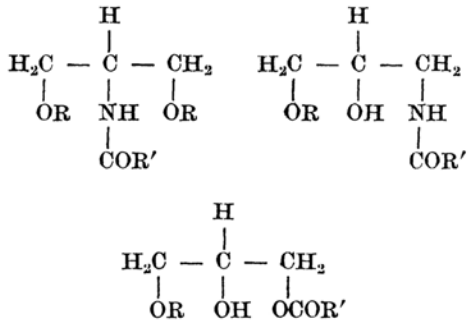
Since the structure of chloramphenicol was proven[1] by a group of workers at the laboratories of Parke Davis & Co. to be *D*-(levo)-threo-2-dichloroacetamido-1-*p*-nitrophenyl-1, 3-propanediol, a number of papers dealing with the preparation of its analogs have appeared, but esterification of the hydroxyl groups of the chloramphenicol type compounds have not been attempted. It might be possible to maintain bacteriostatic activity by dropping off the *p*-nitrophenyl group from the chloramphenicol molecule and by esterifying the hydroxyl groups with *p*-nitrobenzoic or fatty acids of varied chain lengths since certain esters of glycerol[2] have been reported to be active against *Mycobacterium tuberculosis*. As far as we are aware, there have been reported no cases where the haloacylaminopropanediols have been esterified with the acids we used in this experiment.

A number of functional derivatives of the following three types of compounds were prepared (Table 1, 2 and 3).



R=H or acyl group,
R′=haloalkyl group

1- and 2-Aminopropanediols were prepared

Teble 1

1-Aminopropanediol Series, $CH_2(OR)CH(OH)CH_2NHCOCHCl_2$

No.	R	M. P. °C	$n_D^{12.5}$	Calcd. C	Calcd. H	Calcd. N	Found. C	Found. H	Found. N
I	H	59.0—59.5		29.70	4.49	6.93	29.17	4.29	6.78
II	$C_8H_{17}CO$	55.5—56.5 (from absol. MeOH)		49.13	7.36	4.09	48.90	7.70	4.13
III	$C_{11}H_{23}CO$	70.5—71.0 (〃)		53.12	8.13	3.64	53.32	8.36	3.41
IV	p-$O_2NC_6H_4CO$	138.0—138.5 (〃)		41.04	3.44	7.98	41.44	4.01	7.67
V	i-C_3H_7CO	155—170/1.5×10⁻⁴mm.Hg.*	1.492	39.70	5.51	5.15	38.28	5.08	5.39
VI	i-C_4H_9CO	150—170/8×10⁻⁴mm.Hg.*	1.486	41.98	5.99	4.89	43.76	5.91	5.08

* Bath temperature.

Reaction Condition

No.	Reaction time	Yield%	Solubility: MeOH	EtOH	AcMe	Et_2O	AcOH	AcOEt	$CHCl_3$	C_6H_6	Petr. ether	H_2O
II	20 hrs.	27	+	+	+	+	+	+	−	−	−	−
III	24 hrs.	43	+	+	+	+	+	+	+ (hot)	+ (hot)		−
IV	2 weeks	34	+	+	+	−	+	+	+ (hot)	−	−	−
V	24 hrs.	58	+	+	+	+		+	+	−	+ (hot)	−
VI	24 hrs.	65	+	+	+	+		+	+	−	+ (hot)	−

* Part of this work was presented at the Fifth Annual Meeting of the Chemical Society of Japan, April 1952.

(1) M. C. Rebstock, H. M. Crooks, Jr., and J. Controulis, *J. Am. Chem. Soc.*, **71**, 2458, 2163 (1949).

(2) Th. Wagner-Jauregg and H. Arnold, *Ber.*, **70**, 1459 (1937); H. Arnold, ibid., **71**, 1505 (1938); ibid., **73**, 90 (1940).

Table 2

2-Aminopropanediol Series, $CH_2(OR_1)CH(NHCOCHCl_2)CH_2(OR_2)$

No.	R_1	R_2	M. P. °C.*	Calcd. C	Calcd. H	Calcd. N	Found. C	Found. H	Found. N
VII	H	H	143.5—144.0	29.70	4.49	6.93	30.25	5.97	6.84
VIII	$C_8H_{17}CO$	$C_8H_{17}CO$	50.0—51.0	57.24	8.56	2.90	58.34	8.27	2.82
IX	$C_{11}H_{23}CO$	$C_{11}H_{23}CO$	68.5—69.0	61.04	9.42	2.23	60.90	9.22	2.47
X	p-$O_2NC_6H_4CO$	H	141.0—142.0	41.04	3.44	7.98	41.49	3.34	7.67
XI	$C_{15}H_{31}CO$	$C_{15}H_{31}CO$	80.0—81.0	65.46	10.24	2.06	66.21	10.04	2.21
XII	$C_{17}H_{35}CO$	$C_{17}H_{35}CO$	80.0—80.5	66.99	10.56	1.90	67.97	10.39	1.99

* Recrystallized from abs. EtOH.

No.	Reaction time	Yield%	Solubility MeOH	EtOH	AcMe	Et_2O	AcOH	AcOEt	$CHCl_3$	C_6H_6	Petr. ether	H_2O
VIII	3 days	83 (crude)	+	+	+	+			+	−	−	−
IX	3 days	83 (crude)	+	+	+	+			+	−	−	−
X	5 days	73 (crude)	+	+	+	−		+	+	−	−	−
XI	24 hrs.	78 (crude)	+	+	+	+	+		+	−	−	−
XII	24 hrs.	77 (crude)	+	+	+	+	+		+	−	−	−

Table 3

Halogenated Acyl Ester Series, $CH_2(OCOC_{11}H_{23})CH(OH)CH_2(OR)$

No.	R	M. P. °C.	Calcd. C	Calcd. H	Found. C	Found. H
XIII	$CHCl_2CO$	175—178/10^{-2}mm.Hg.*	52.90	7.84	52.61	7.50
XIV	CH_2ClCO	50.0—50.5 145—155/10^{-2}mm.Hg.*	58.19	8.19	58.57	8.78

* Bath temperature.

No.	Reaction time	Yield%	Solubility MeOH	EtOH	AcMe	Et_2O	AcOEt	$CHCl_3$	C_6H_6	Petr. ether	H_2O
XIII	24 hrs.	82	+	+	+	+	+	+	−	−	−
XIV	24 hrs.	68	+	+	+	+	+	+	−	−	−

according to the method described in the literature.[3~5] The amino group was acylated first with methyl dichloroacetate and then one or both hydroxyl groups were esterified with long chain aliphatic acids or p-nitrobenzoic acid.

Since it has been observed that the acyl migration[6][7] takes place from the oxygen of the hydroxyl group to the nitrogen of the amino group in acyl derivatives of the aminopropanediol in an alkaline solution and vice-versa in an acid solution, the confirmation of the chemical costitution of the final compounds prepared was desirable. If the 2-hydroxyl group in the 1-acyl-amino-2, 3-propanediol and the 1, 3-hydroxyl groups in the 2-acyl-amino isomer were left free, the migration of the acyl group from the nitrogen of the amino group to the oxygen of the hydroxyl groups to the 2- and 1 or 3-posititions, respectively, would occur on treatment with phosphorus pentachloride. Therefore, the hydroxyl groups were acylated previous to the treatment with

(3) E. Abderhalden and E. Eichwald, *Ber.*, **47**, 2888 (1913).
(4) E. Schmidt and R. Wilkendorf, *ibid.*, **52**, 398 (1919).
(5) H. Schlenk and B. W. De Haas, *J. Am. Chem. Soc.*, **73**, 3921 (1951).
(6) Max Bergmann and S. Sabetay, *Z. physical. Chem.*, **137**, 47 (1924).
(7) Carlo G. Alberti, XII Int. Congr. Meeting in New York, Sept., 1951.

phosphorus pentachloride. 1-Dichloroacetamido-3-lauroyloxy-2-propanol was esterified with stearoyl chloride and the resulting product was treated with phosphorus pentachloride,[8] followed by deamination with nitrous acid to give 1-lauroyl-2-stearoylglycerol, which was then esterified with stearoyl chloride. The final product melted at 56.0~57.0°C. and showed no depression of its m. p. when mixed with an authentic sample (m. p. 54.0°C.[9]) prepared according to Fischer's method.[10] Similarly, deamination was carried out with 2-dichloroacetamido-1, 3-dilauroyloxypropane.

This procedure proves that no migration of the dichloacetyl group or no interchange of the haloacyl with other acylgroup has taken place. The preparation of 1-lauroyloxy-2, 3-distearoyloxy from 1-dichloroacetamido-3-lauroyloxy-2-propanol shows that the monoacylation of the primary alcohol has taken place during the acylation of the haloacylaminopropanediol. Therefore, it is reasonable to state that the rest of the compounds prepared possess the structures as indicated.

Experimental

dl-Dichloroacetamidopropanediol (I).—A mixture of 18 g. (0.197 mol) of 1-aminopropanediol (140~140.5°C./6~6.5 mm) and 30 g. (0.209 mol) of methyl dichloroacetate was refluxed on the water bath for 1½ hrs. The methanol formed was removed and the residue was washed by decantation five times with 30 cc. portions of petroleum ether and dried over conc. sulfuric acid paraffin in a vacuum desiccator to induce crystallization. The crude product was dissolved in ethyl acetate, the solution filtered, the solvent removed and the residue washed with petroleum ether. The yield was quantitative.

1-Dichloroacetamido-3-lauroyloxy-2-propanol (III).—To a mixture of 8 g. (0.039 mol) of dl-dichloroacetamidopropanediol, 30 cc. of chloroform and 4 g. of pyridine, cooled to zero degree, was added dropwise 8 g. (0.037 mol) of lauroyl chloride* under constant stirring. The reaction mixture was allowed to stand at room temperature for 24 hrs., acidified with 1/2 N sulfuric acid and extracted with ether. The ether extract washed with a 5% solution of sodium carbonate followed by water and dried over anhydrous sodium sulfate. It was then filtered and the residue obtained after removal of the solvent was allowed to stand at −18°C. to allow crystallization to take place. The crude product was dried in a vacuum desiccator over conc. sulfuric acid, and purified by recrystallization from absolute methanol. The crude product weighed 10 g. (71% of theoretical yield), and pure product melting at 70.5~71.0°C. weighed 6 g. (43% of theoretical yield). The compounds 1-dichloroacetamido-3-nonoyloxy-2-propanol (II) and 1-dichloroacetamido-3-*p*-nitrobenzoloxy-2-propanol (IV) were prepared by the similar method described above.

dl-1-Dichloroacetamido-3-isobutyroyloxy-2-propanol (V).—To a solution of 6 g. (0.029 mol) of dl-dichloroacetamidopropanediol and 3 g. of pyridine in 5 cc. of chloroform was added, under cooling, 3.5 g. (0.026 mol) of isobutyroyl chloride and allowed to stand at room temperature for 24 hrs. The reaction mixture was treated in the manner similar to the method described for the preparation of 1-dichloroacetamido-3-lauroyloxy-2-propanol. Since it was found to be a liquid compound, the crude product was extracted with ether, the solvent removed, the residue extracted with alcohol, and the residue obtained after removing the alcohol was subjected to high vacuum distillation.

The 1-dichloroacetamido-3-isovaleroyloxy-2-propanol (VI) was prepared similarly.

1-Lauroyloxy-2, 3-distearoyloxypropane.—For the confirmation of the structure of 1-dichloroacetamido-3-lauroyloxy-2-propanol, one gram (0.0026 mol) of 1-dichloroacetamido-3-lauroyloxy-2-propanol was dissolved in a mixture of 10 cc. of chloroform and 2.5 g. of pyridine, the resulting mixture treated, under cooling, with 0.85 g. (0.0028 mol) of stearoyl chloride and the reaction mixture allowed to stand for 2 days. The subsequent treatment of the reaction mixture was carried out in the manner similar to the method described previously. The pure compound melted at 66~67°C.

The compound thus obtained was treated with phosphorus pentachloride according to the method described in the literature[8] to obtain the hydrochloride salt of 1-amino-2-stearoyloxy-3-lauroyloxypropane. The product was then deaminated with nitrous acid to give 1-lauroyl-2-stearoyl glycerol, which was then esterified with stearoyl chloride in the presence of pyridine. The purified triglyceride melting at 56.0~57.0°C. showed no depression of its melting point when mixed with the sample prepared according to Fischer's method.[10] (Reported m. p. 54.0°C.[9])

The total amount of lauric acid obtained by hydrolysis of 1-dichloroacetamido-3-lauroyloxy-2-propanol with 0.1 N sodium hydroxide was found quantitative.

2-Dichloroacetamidopropanediol (VII).—2-Aminopropanediol[5] was treated with methyl dichloroacetate in the manner described for the preparation of the dl-dichloroacetamido isomer. The crude product was purified once from a mixture of methanol and petroleum ether and then from absolute alcohol, m. p. 143.5−144.0°C. The yield was quantitative.

(8) Max Bergmann, E. Brand and F. Dreyer, *Ber.*, **54**, 933 (1921).

(9) B. F. Daubert, *J. Am. Chem. Soc.*, **66**, 291 (1944). Daubert prepared this compound by the reduction of 1-lauroyloxy-2, 3-dielaidoyloxypropane.

(10) E. Fischer, *Ber.*, **53**, 1589 (1920).

* Lauric acid used in this experiment was a c. p. grade of Matheson product.

2-Dichloroacetamido-1, 3-dilauroyloxypropane (IX).—A solution of 1.2 g. (0.0060 mol) of 2-dichloroacetamidopropanediol in a mixture of 30 cc. chloroform and 10 g. of pyridine was treated, under cooling, with 1.8 g. (0.0082 mol) of lauloyl chloride, the reaction mixture allowed to stand for three days, and treated in the manner described for the preparation of 1-dichloroacetamido-3-lauroyloxy-2-propanol. Compounds 2-dichloroacetamido-1, 3-dinonoyloxypropane (VIII), 2-dichloroacetamido-1-*p*-nitrobenzoyloxy-3-propanol (X), 2-dichloroacetamido-1, 3-dipalmitoyloxypropane (XI),* 2-dichloroacetamido-1, 3-distearoyloxypropane (XII),* were prepared according to the method mentioned above.

1-Chloroacetyl-3-lauroyl glycerol (XIV).—A solution of 4.5 g. (0.016 mol) of monolaurin (m. p. 62～63°C)[10] and 1.5 g. of pyridine in 15 cc. of chloroform was treated, under cooling, with 2.5 g. (0.022 mol) of monochloroacetyl chloride and the resulting reaction mixture was worked up as described previously. The product was taken up in ether, the solvent removed, and the residue subjected to high vacuum distillation.

Compound 1-dichloroacetyl-3-lauroyl glycerol (XIII) was prepared in the similar manner.

1, 3-Dilaurin.—Upon treatment of compound 2-dichloroacetamido-1, 3-dilauroyloxypropane with phosphorus pentachloride followed by nitrous acid, as described for the 1-compound, 1, 3-dilauryl glycerol, m. p. 56～57°C. was obtained. This product showed no depression of its melting point when mixed with the sample (m. p. 56～57°C.) prepared according to the method of Daubert[11] (reported m. p. 58°C.). The hydrolysis of 2-dichloroacetamido-1, 3-dilauroyloxypropane with 0.1 N NaOH gave quantitative recovery of lauric acid.

* Palmitic and stearic acids used were c. p. grades obtained from the "Delta Chemical Works", m. p. 61-62°C and 68-69°C, respectively.

Summary

Derivatives of 1-aminopropanediol, 2-aminopropanediol and the halogenated acyl esters of glycerol have been prepared. The amino group has been acylated with haloalkylacyl group and one or both hydroxyl groups with aliphatic acids of various chain lengths. Preliminary experimental results have shown that these compounds exhibit bacteriostatic activity in vitro against mycobacterium tuberculosis, avian. The chemical constitution of the isomeric products, the 1-amino and 2-amino derivatives, has been confirmed. The preparation of the optical active forms of the aminopropanediols are now in progress.

Osaka City University, Department of Home Economics, Osaka

(11) B. F. Daubert, *J. Am. Chem. Soc.*, **66**, 289 (1944).