TABLE IV

1-AZA-2,8-DIALKYL-5-HYDROXYMETHYL-3,7-DIOXABICYCLO(3.3.0)OCTANES,[a] $HOCH_2-C(CH_2O-)(-N<)(-CHR)(-CHR)$

R	Yield, %	B.p. (uncor.) °C.	Mm.	Nitrogen, % Calcd.	Found	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
H[b]	77	59–60[c]							
n-C_3H_7[d]	75	112.5–113.5	0.2	6.11	6.10				
n-C_5H_{11}	84	216–217	32	4.91	5.00	67.37	67.35	10.87	10.68
		151–153	0.3						
C_6H_5[e,f]	85	93–95		4.71	4.92	72.72	72.90	6.39	6.50
$C_6H_5CH_2$	56	238–240	1.0	4.31	4.38	73.84	73.61	7.07	7.10

[a] In one case, R is phenyl. [b] First prepared by Senkus.[6] [c] M.p. [d] To a mixture of 12.1 g. (0.1 mole) of (A) and 80 ml. of benzene was added 14.4 g. (0.2 mole) of n-butyraldehyde. The mixture was refluxed for 6 hours under a water separator while 3.6 ml. of water was collected. The benzene was removed on a water-bath under vacuum and the residue was vacuum distilled. The product, 1-aza-5-hydroxymethyl-2,8-di-n-propyl-3,7-dioxabicyclo(3.3.0)octane boiled at 179.5–182° (32 m.m.); yield 17.2 g., 75% of theory. [e] Recrystallized from butyl ether and from cyclohexane. 1-Aza-5-hydroxymethyl-2,8-diphenyl-3,7-dioxabicyclo(3.3.0)octane was precipitated as the hydrochloride by solution of the free base in ether and addition of alcoholic hydrogen chloride. The hydrochloride was purified to constant melting point by solution in alcohol and precipitation with ether; m.p. 130–131°. On exposure of a freshly purified sample for 10 minutes on a clay plate, the odor of benzaldehyde was pronounced. *Anal.* Calcd. for $C_{18}H_{20}ClNO_3$: Cl, 10.70. Found: Cl, 10.81.

(A).[6] By loss of two moles of water between two moles of an aldehyde and one mole of (A)[6,7] 1-aza-3,7-dioxabicyclo(3.3.0)octanes are formed. Thus, equimolar quantities of n-butyraldehyde and (A) yield 2-propyl-4,4-bis-(hydroxymethyl)-oxazolidine, $(HOCH_2)_2C(-NH-)(-CHC_3H_7)(-CH_2O-)$, while two moles of n-butyraldehyde and one mole of (A) yield 1-aza-2,8-dipropyl-5-hydroxymethyl-3,7-dioxabicyclo(3.3.0)-octane, $HOCH_2-C(CH_2O-)(-N<)(-CHC_3H_7)(-CHC_3H_7)$.

Purification may be effected by vacuum distillation in most cases. The crystalline oxazolidines and bicyclic compounds prepared in this study are purified by recrystallization from acetone, butyl ether, hexane or cyclohexane.

(6) Senkus, THIS JOURNAL, **67**, 1515 (1945).

(7) American Cyanamid Co., British Patent 564,506 (1944).

RICHMOND, VIRGINIA RECEIVED MARCH 13, 1950

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

Tris-(hydroxymethyl)-aminomethane Derivatives. IV. Substituted 4-Hydroxymethyloxazolidines; Ester and Amide Interchange[1]

BY J. STANTON PIERCE AND CARL D. LUNSFORD

Monoacyl derivatives of tris-(hydroxymethyl)-aminomethane (I) have been prepared by the hydrolysis of monoacyl derivatives of 1-aza-5-hydroxymethyl-2,8-diphenyl-3,7-dioxabicyclo(3.3.0)octane (II), and by the hydrolysis of 4,4-bis-(hydroxymethyl)-2-substituted oxazolines (IX). Ester–amide interchange has been studied with the monoacyl derivatives of (I) and the intermediate substituted oxazolidines.

Controlled monoacylation of tris-(hydroxymethyl)-aminomethane (I) is very difficult, due to the plurality of functional groups, the resultant high polarity and low solubility in inert solvents. This work was undertaken to prepare monoacyl derivatives of (I) by the use of cyclic intermediates in which two or more of the functional groups are in combination. 1-Aza-5-hydroxymethyl-2,8-diphenyl-3,7-dioxabicyclo(3.3.0)octane (II) and 4,4-bis-(hydroxymethyl)-2-substituted oxazolines (IX) proved to be the most useful intermediates for this purpose. These compounds, (II) and (IX), are prepared by heating (I) with two moles of benzaldehyde[2] and with an equimolar amount of an organic acid,[3] respectively.

The series of reactions involved in this study is given in Fig. 1. Each reaction was completed with one or more acyl groups.

On treatment of (II) with acid chlorides, usually gummy masses are formed. However, from the reaction of p-nitrobenzoyl chloride and (II) there was isolated crystalline, hygroscopic 1-aza-5-p-nitrobenzoyloxymethyl-2,8-diphenyl-3,7-dioxabicyclo-(3.3.0)octane hydrochloride.

The 4-acyloxymethyl-4-hydroxymethyl-2-phenyloxazolidine hydrochloride (IV) was obtained by the hydrolysis of the reaction product of II and an acid chloride. Addition of nitrate ion to a water solution of IV readily converted the hydrochloride to the corresponding nitrate V. All of the nitrates isolated were relatively insoluble in water.

By making an aqueous solution of the 4-acyloxymethylhydroxymethyl-2-phenyloxazolidine hydrochloride basic with sodium hydroxide or sodium carbonate, the 3-acyl-4,4-bis-(hydroxymethyl)-2-

(1) (a) This research was supported by a grant from the Office of Naval Research; (b) acknowledgment is made to Dr. Emmet Reid, Research Adviser to the Chemistry Department of the University of Richmond, for his advice in this work.

(2) J. S. Pierce, C. D. Lunsford, R. W. Raiford, J. L. Rush and D. W. Wiley, THIS JOURNAL, **73**, 2595 (1951).

(3) J. H. Billman and E. E. Parker, *ibid.*, **67**, 1070 (1945).

phenyloxazolidine (VI) was obtained as a heavy precipitate. In this operation an intermediate alkali-soluble substance was formed in some cases. This was indicated by precipitation when the base was first added, followed by momentary solution and finally precipitation of the crystalline N-acyl oxazolidine. This solubility apparently supports the mechanism for the O→N acyl migration presented by Fodor and Kiss.[4] The N-acyl oxazolidine (VI) also was obtained by making basic a solution of the oxazolidine nitrate (V).

This O→N acyl migration also extends the generality of the reaction to β-aminoalcohols having the nitrogen as a member of a heterocyclic ring. The shift occurred rapidly for cases in which the acyl group was acetyl, phenoxyacetyl and *p*-nitrobenzoyl. When the acyl group was caproyl, addition of alkali liberated the free base of the ester as an oil readily soluble in dilute acid but which on standing for three days, followed by recrystallization from cyclohexane, gave a 72% yield of the acid insoluble amide. When the acyl group was benzoyl, the migration could not be demonstrated conclusively.

Treatment of VI with alcoholic hydrogen chloride resulted in the cleavage of the oxazolidine ring and the formation of 2-amino-3-hydroxy-2-hydroxymethylpropyl ester hydrochlorides VII, the acyl group having migrated back to oxygen. The latter transformation was accomplished when the acyl group was *p*-nitrobenzoyl and phenoxyacetyl. The latter ester hydrochloride was readily converted to the corresponding N-[2-hydroxy-1,1-bis-(hydroxymethyl)-ethyl] amide (VIII), on making the aqueous solution basic.

Where R is phenyl or phenoxymethyl, the ester hydrochloride VII was prepared from the corresponding 4,4-bis-(hydroxymethyl) 2-substituted oxazoline (IX), which in turn was prepared from (A) and the acid, RCOOH.

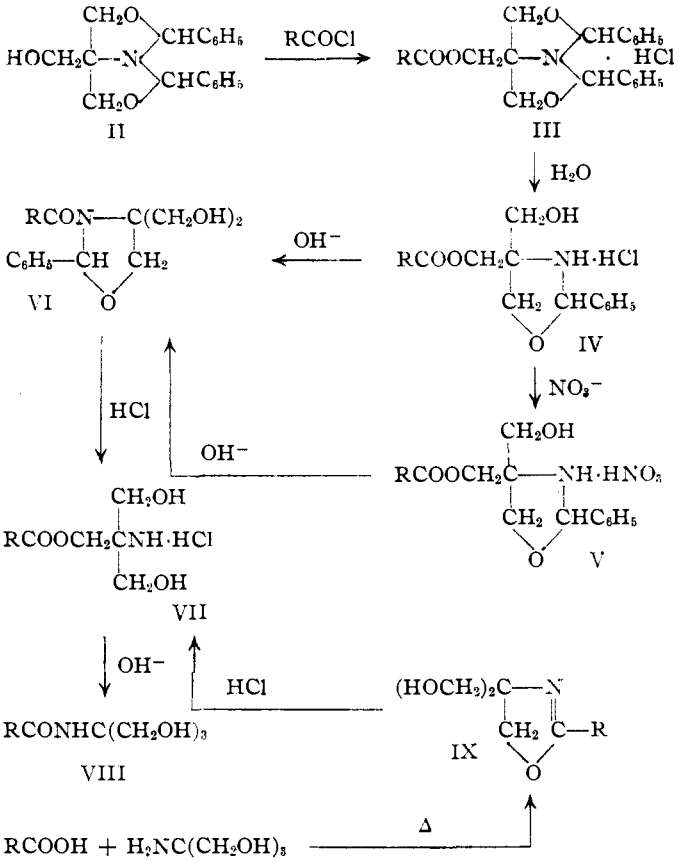


Fig. 1.

Experimental[5]

5-Acyloxymethyl-1-aza-2,8-diphenyl-3,7-dioxabicyclo-(3.3.0)octane Hydrochlorides[6] (III).—A benzene solution of equimolar quantities of 1-aza-5-hydroxymethyl-2,8-diphenyl-3,7-dioxabicyclo(3.3.0)octane and *p*-nitrobenzoyl chloride was refluxed for five hours. The oil which separated, on cooling, was converted to a crystalline, hygroscopic solid, by stirring with dry ether. Without purification, this product gave a chloride analysis corresponding to that required for 1-aza-5-*p*-nitrobenzoyloxymethyl-2,8-diphenyl-3,7-dioxabicyclo(3.3.0)octane hydrochloride.

Anal. Calcd. for $C_{25}H_{23}O_6N_2Cl$: Cl, 7.34. Found: Cl, 6.91.

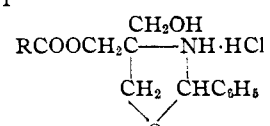
In all other preparations in this study, the 5-acyloxymethyl-1-aza-2,8-diphenyl-3,7-dioxabicyclo(3.3.0)octane hydrochlorides were obtained as gums.

4-Acyloxymethyl-4-hydroxymethyl-2-phenyloxazolidine Hydrochlorides (IV).—To a solution of 0.10 mole of 1-aza-5-hydroxymethyl-2,8-diphenyl-3,7-dioxabicyclo(3.3.0)octane in 50 ml. of benzene was added 0.10 mole of acid chloride. The solution was heated or allowed to stand, depending on the acid chloride, as indicated in Table I. After cooling, enough dry ether was added to cause complete separation of a heavy oil which in most cases came out of the benzene solution. The solvents were decanted and the oil was stirred with several portions of dry ether. The preparation was completed according to one of the following methods.

Method (A).—The oil was added to 100 ml. of water and the mixture heated on the steam-bath for 30 minutes, after which it was cooled and extracted with ether. The ex-

TABLE I

4-ACYLOXYMETHYL-4-HYDROXYMETHYL-2-PHENYLOXAZOLIDINE HYDROCHLORIDES



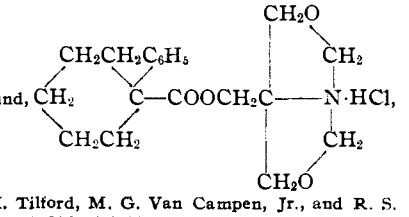
R	Method	M.p., °C. (uncor.)	Yield, %	Chlorine, % Calcd.	Found
CH_3	B	170–171[a]	49	12.32	12.14
C_5H_{11}[b]	B	134–135[c]	28	10.31	10.24
C_6H_5[d]	B	188–189	17	10.13	9.94
p-$O_2NC_6H_4$[d]	B	158–159[a]	19	8.98	8.57
$C_6H_5OCH_2$[e]	A	150–152	27	9.34	9.09

[a] After recrystallization from absolute ethanol. [b] Refluxed 2.5 hours. [c] After recrystallization from acetone–petroleum ether mixture. [d] Refluxed 5 hours. [e] Refluxed 1 hour.

(4) G. Fodor and J. Kiss, THIS JOURNAL, **72**, 3495 (1950).

(5) We wish to express acknowledgment to Dr. R. S. Murphey for his suggestions and to Mr. J. L. Rush and Mr. Theodore Katz for the preparation of starting compounds and for analytical work.

(6) A similar compound,



was prepared by C. H. Tilford, M. G. Van Campen, Jr., and R. S. Shelton, THIS JOURNAL, **69**, 2906 (1947).

traction was repeated, the aqueous layer being made basic after the ether was added. The ether layer in some cases immediately began to yield crystalline 3-acyl-4,4-bis-(hydroxymethyl)-2-phenyloxazolidine. The precipitate was removed by filtration and the filtrate was allowed to pass into ethereal or alcoholic hydrogen chloride, thus yielding the crystalline hydrochloride.

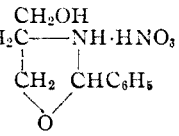
Method (B).—The oil was dissolved in a minimum quantity of cold acetone. Two ml. of water was added and the solution was allowed to stand. The crystalline product separated from solution within 30 minutes.

Purification was effected by recrystallization from ethanol, butanol, or an acetone–petroleum ether mixture.

4-Acyloxymethyl-4-hydroxymethyl-2-phenyloxazolidine Nitrates (V).—To an aqueous solution of the 4-acyloxymethyl-4-hydroxymethyl-2-phenyloxazolidine hydrochloride was added 1:1 nitric acid until no further precipitation occurred. The white crystalline ozazolidine nitrates were recrystallized from ethyl alcohol.

TABLE II

4-ACYLOXYMETHYL-4-HYDROXYMETHYL-2-PHENYLOXAZOLIDINE NITRATES



R	M.p., °C.[a] (uncor.)	Yield, %	Nitrogen, % Calcd.	Found
CH_3	158–160	73	8.91	9.10
C_5H_{11}	144–145	11	7.56	7.60
p-$O_2NC_6H_4$	179–181	78	9.97	9.92
$C_6H_5OCH_2$	166–167	81	6.89	7.20

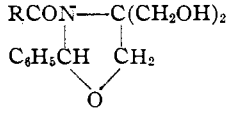
[a] After recrystallization from ethyl alcohol.

3-Acyl-4,4-bis-(hydroxymethyl)-2-phenyloxazolidines (VI).—An aqueous solution of the 4-acyloxymethyl-4-hydroxymethyl-2-phenyloxazolidine hydrochloride was made basic with sodium carbonate solution. When the acyl group was phenoxyacetyl, p-nitrobenzoyl or acetyl, precipitation occurred immediately or on stirring the solution. In some cases the initial precipitation was followed by momentary solution and then by reprecipitation.

When the acyl group was caproyl, the basic solution was extracted with ether and the ether evaporated. The oily residue was readily soluble in dilute acid but after standing three days, yielded some crystalline solid, insoluble in acid. The mixture, oil and solid, on solution in hot cyclohexane and cooling, yielded the crystalline amide, which was filtered off. On evaporation of the filtrate and allowing it to stand, more crystalline amide was formed.

TABLE III

3-ACYL-4,4-BIS-(HYDROXYMETHYL)-2-PHENYLOXAZOLIDINES



R	M.p., °C. (uncor.)	Yield, %	Nitrogen, % Calcd.	Found
CH_3	120–122[a]	68	5.58	5.66
C_5H_{11}	118–119[b]	72	4.56[c]	4.51
p-$O_2NC_6H_4$	132–134[a]	80	7.82	8.10
$C_6H_5OCH_2$	143–145[a]	74	4.08[d]	4.13

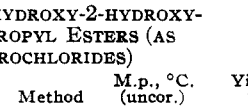
[a] After recrystallization from butanol. [b] After recrystallization from cyclohexane. [c] *Anal.* Calcd. for $C_{17}H_{25}O_4N$: C, 66.45; H, 8.13. Found: C, 66.20; H, 8.17. [d] *Anal.* Calcd. for $C_{19}H_{21}O_5N$: C, 66.47; H, 6.12. Found: C, 66.32; H, 6.40.

2-Amino-3-hydroxy-2-hydroxymethylpropyl Ester Hydrochlorides (VII). Method (A).—To a solution of 0.05 mole of 4,4-bis-(hydroxymethyl)-2-substituted oxazoline in 150 ml. of absolute alcohol was added 10 ml. of concentrated hydrochloric acid and the solution was allowed to stand for one-half hour. Addition of dry ether caused the precipitation of crystalline ester hydrochloride VII in some cases. In other cases the solution was heated on the hot-plate for 15 minutes and then evaporated to low volume under vacuum; the residue then was taken up in hot butanol which yielded a crystalline product on cooling.

Method (B).—A solution of the 3-acyl-4,4-bis-(hydroxymethyl)-2-phenyloxazolidine in alcoholic hydrogen chloride was formed by warming the mixture. The solution was allowed to stand about two hours. The crystalline product was isolated either by addition of dry ether, which caused precipitation of the product, or by evaporation of the solution to low volume under reduced pressure and treatment of the residue with ether, which caused crystallization.

TABLE IV

2-AMINO-3-HYDROXY-2-HYDROXYMETHYLPROPYL ESTERS (AS HYDROCHLORIDES)



R	Method	M.p., °C. (uncor.)	Yield, %	Chlorine, % Calcd.	Found
C_6H_5	A	200–202[a]	37	13.55	13.42
$C_6H_5OCH_2$	A	170–173[b]	69	12.15	11.78
	B		87		
p-$O_2NC_6H_4$	B	205–207[b]	95	11.56	11.54

[a] After recrystallization from ethanol. [b] After recrystallization from butanol.

N-[2-Hydroxy-1,1-bis-(hydroxymethyl)-ethyl]-phenoxyacetamide (VIII).—A solution of 2-amino-3-hydroxy-2-hydroxymethylpropyl phenoxyacetate hydrochloride was made basic with sodium hydroxide. On stirring the solution for less than three minutes the amide formed as a heavy precipitate, and was recrystallized from butanol; m.p. 141–143°; yield 52%.

Anal. Calcd. for $C_{12}H_{17}O_5N$: N, 5.49. Found: N, 5.58.

4,4-Bis-(hydroxymethyl)-2-substituted Oxazoline.—A mixture of one mole of the acid and one mole of (A) in 1000 ml. of xylene was refluxed until the required amount of water was removed with a water trap. Cooling of the resulting solution caused separation of the product, usually an oil which crystallized on cooling further. Recrystallization was effected from ethanol or acetone. The 2-phenyl derivative[3] and the 2-phenoxymethyl derivative were prepared. The latter was recrystallized from ethanol; m.p. 139–140°; yield 53%.

Anal. Calcd. for $C_{12}H_{15}O_4N$: N, 5.91. Found: N, 5.84.

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