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

Tris-(hydroxymethyl)-aminomethane Derivatives. III. Oxamides, Ureas, Oxazolidines and 1-Aza-3,7-dioxabicyclo(3.3.0)octanes[1]

BY J. STANTON PIERCE, CARL D. LUNSFORD, R. W. RAIFORD, JR., J. L. RUSH AND DOUGLAS W. RILEY

Tris-(hydroxymethyl)-aminomethane, $(HOCH_2)_3CNH_2$ (A), reacts with ethyl oxalate to form crystalline N,N'-bis-[tris-(hydroxymethyl)-methyl]-oxamide and with ethyl N-aryloxamates to yield unsymmetrical oxamides of the structure, $ArNHCOCONHC(CH_2OH)_3$. With aryl isocyanates, N-aryl-N'-[tris-(hydroxymethyl)-methyl]-ureas are formed. (A) reacts with equimolar quantities of aldehydes to yield 4,4-bis-(hydroxymethyl)-2-substituted-oxazolidines; with two moles of aldehydes 5-hydroxymethyl-2,8-disubstituted-1-aza-3,7-dioxabicyclo(3.3.0)octanes are formed.

In a previous study of tris-(hydroxymethyl)-aminomethane (A) in this Laboratory, alkylation products[2] and polyhydroxyamines[3] were prepared. The present study includes the reactions of (A) with ethyl oxalate, ethyl-N-aryloxamates, arylisocyanates and aldehydes.

Ethyl oxalate, on being heated with (A), yields N,N'-bis-[tris-(hydroxymethyl)-methyl]-oxamide, $(HOCH_2)_3CNHCOCONHC(CH_2OH)_3$. N-Aryl-N'-[tris-(hydroxymethyl)-methyl]-oxamides are prepared by heating ethyl N-aryloxamates[4] with (A). Thus, the condensation of equimolar quantities of aniline and ethyl oxalate yields ethyl-N-phenyloxamate,[5] which on being heated with an equivalent quantity of (A) yields N-phenyl-N'-[tris-(hydroxymethyl)-methyl]-oxamide, $C_6H_5NHCOCONHC(CH_2OH)_3$.

Equimolar quantities of aryl isocyanates and (A), when heated for a short time in chloroform solution or in the absence of a solvent, yield N-aryl-N'-[tris-(hydroxymethyl)-methyl]-ureas, which may be recrystallized from 1-butanol or water–ethanol solution. For example, when phenyl isocyanate and (A) are refluxed in chloroform solution, the product which separates on cooling is N-phenyl-N'-[tris-(hydroxymethyl)-methyl]-urea, $C_6H_5NHCONHC(CH_2OH)_3$.

TABLE I

N-SUBSTITUTED-N'-[TRIS-(HYDROXYMETHYL)-METHYL]-OXAMIDES, $RNHCOCONHC(CH_2OH)_3$

R	Yield, %	M. p., °C. (uncor.)	Nitrogen, % Calcd.	Nitrogen, % Found
$(HOCH_2)_3C$	30	210–212	9.46	9.72
C_6H_5[a]	52	174.5–177	10.44	10.70
p-$CH_3C_6H_4$	78	170.0–170.5	9.93	10.18
β-$C_{10}H_7$	85	162–163.5	8.80	8.69
α-$C_{10}H_7$	73	170–172	8.80	8.88
o-$CH_3OCOC_6H_4$	52	165–168	8.59	8.73
p-$C_2H_5OCOC_6H_4$	80	175.5–176	8.23	8.30

[a] Equimolar amounts of aniline and ethyl oxalate were heated at approximately 115° for 5.5 hours. The reaction mixture was extracted with boiling alcohol, acidified with hydrochloric acid and filtered while hot from N,N'-diphenyloxamide. On cooling the filtrate, filtering and recrystallizing the precipitate from hot water, ethyl-N-phenyloxamate,[5] m.p. 63–67°, was obtained in 74% yield. After recrystallization from ethanol, the m.p. was 66–67°. An ethanol solution of equimolar amounts of ethyl-N-phenyloxamate and (A) was refluxed for 30 minutes. On cooling, filtering and recrystallizing from boiling water, N-phenyl-N'-[tris-(hydroxymethyl)-methyl]-oxamide was obtained in 52% yield.

Oxazolidines are formed by loss of one mole of water between molar quantities of an aldehyde and

TABLE II

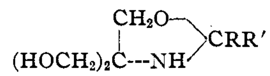
N-ARYL-N'-TRIS-(HYDROXYMETHYL)-METHYLUREAS, $RNHCONHC(CH_2OH)_3$

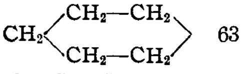
R	Yield, %	M. p., °C. (uncor.)	Nitrogen, % Calcd.	Nitrogen, % Found
C_6H_5[a]	70	194–195	11.66	11.88
o-$CH_3C_6H_4$[b]	81	194–195	11.02	11.31
p-$CH_3C_6H_4$[b]	87	192–193	11.02	11.15
α-$C_{10}H_7$[a]	97	213–215	9.65	10.03
β-$C_{10}H_7$[b]	90	200–201	9.65	9.68

[a] Equimolar amounts of (A) and aryl isocyanate were heated gently for 10 minutes and the reaction mixture was stirred with chloroform and filtered. The residue was recrystallized from aqueous ethanol. [b] A chloroform solution of aryl isocyanate and suspension of an equimolar amount of (A) was boiled for 15 minutes. The chloroform insoluble residue was recrystallized from n-butyl alcohol.

TABLE III

2-SUBSTITUTED-4,4-BIS-(HYDROXYMETHYL)-OXAZOLIDINES



R	R'	Yield, %	B.p. (uncor.) °C.	B.p. (uncor.) Mm.	Nitrogen, % Calcd.	Nitrogen, % Found
H	n-C_3H_7[a]	45	195–206	34	7.98	8.35
H	C_6H_5	58	185–189	0.5	6.70	6.90
		63	118.1–120[b]		6.96	7.22
H	$C_6H_5CH_2$	20	188–198	1.0	6.27	6.30

[a] In a typical experiment, 12.1 g. (0.1 mole) of (A), 7.2 g. (0.1 mole) of n-butyraldehyde and 80 ml. of benzene were refluxed 8 hours under a water separator. Approximately 2.0 ml. of water separated. To the reaction mixture was added 50 ml. of acetone and the unreacted (A) was filtered off. The acetone and benzene were removed on a water-bath under vacuum and the residue was vacuum distilled. There was obtained 4.7 g. (45% of theory) of oily 2-n-propyl-4,4-bis-(hydroxymethyl)-oxazolidine, b.p. 195–206 (34 mm.), which became very pasty on standing in a desiccator overnight. In cases when reaction did not take place readily at the boiling point of benzene, xylene was used to remove water. [b] M.p. of 2-spiro-(cyclohexyl)-4,4-bis-(hydroxymethyl)-oxazolidine, after recrystallization from anhydrous acetone. This compound was prepared by the reaction of cyclohexanone and (A), in xylene. 2-Spiro-(cyclohexyl)-4,4-bis-(hydroxymethyl)-oxazolidine hydrochloride was prepared by dissolving the free base in absolute alcohol and saturating with hydrogen chloride. The product was precipitated by the addition of ether and was purified to constant melting point by solution in absolute ethanol, saturation with hydrogen chloride and precipitation with ether; m.p. 170–171°.

Anal. Calcd. for $C_{10}H_{20}ClNO_3$: Cl, 14.77. Found: Cl, 14.53.

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

(2) J. S. Pierce and John Wotiz, THIS JOURNAL, **73**, 2594 (1951).

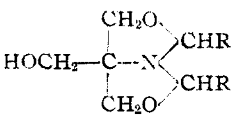
(3) J. S. Pierce and John Wotiz, *ibid.*, **66**, 879 (1944).

(4) Chattaway and Lewis, *J. Chem. Soc.*, **89**, 155 (1906); Chattaway and Clemo, *ibid.*, **109**, 89 (1916).

(5) Klinger, *Ann.*, **184**, 263 (1877).

TABLE IV

1-AZA-2,8-DIALKYL-5-HYDROXYMETHYL-3,7-DIOXABICYCLO(3.3.0)OCTANES,[a]

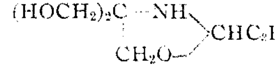


$$HOCH_2-\overset{CH_2O}{\underset{CH_2O}{C}}-N\left\langle\begin{matrix}CHR\\CHR\end{matrix}\right.$$

R	Yield, %	B.p. (uncor.) °C.	Mm.	Nitrogen, % Calcd.	Nitrogen, % Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % 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[a,e]	85	93–95[c]		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

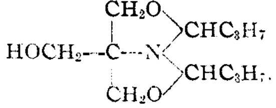
[a] In one case, R is phenyl. [b] First prepared by Senkus.[6] [c] M.p. [d] To a mixture of 12.1 g. (0.1 mole) of (A) and 80 ml. of benzene was added 14.4 g. (0.2 mole) of n-butyraldehyde. The mixture was refluxed for 6 hours under a water separator while 3.6 ml. of water was collected. The benzene was 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 mm.); 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,



$$\begin{matrix}(HOCH_2)_2C-NH\diagdown\\ \qquad\qquad\qquad\quad CHC_3H_7,\\ CH_2O-\diagup\end{matrix}$$

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,



$$HOCH_2-\overset{CH_2O}{\underset{CH_2O}{C}}-N\left\langle\begin{matrix}CHC_3H_7\\CHC_3H_7.\end{matrix}\right.$$

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).

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

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

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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-

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(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).