1,3-Diacyl Derivatives of Imidazolidine and Hexahydropyrimidine: I. Preparation by Novel Method and Characterization[1]

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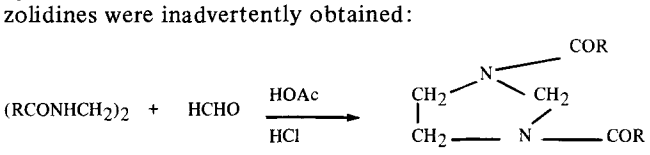
ABSTRACT

The reaction of formaldehyde and diamides of 1,2-diamines in acetic acid containing a trace of hydrochloric acid was found to give 1,3-diacyl derivatives of imidazolidine in high yield. The similar reaction of formaldehyde and diamides of 1,3-propylenediamine gave high yields of 1,3-diacylhexahydropyrimidines. Attempts to extend this reaction to other aldehydes than formaldehyde failed, as did attempts to condense formaldehyde with a diamide which would give a four-membered or seven-membered ring system, the diamide being recovered unchanged in each instance. Twenty-two new compounds were prepared and characterized.

INTRODUCTION

Substituted hexahydropyrimidines are readily prepared by the reaction of aldehydes or ketones with 1,3-diamines (1-3). A similar reaction employing 1,2-diamines yields the analogous imidazolidines (4,5). A variety of uses have been claimed for substituted derivatives containing either of these two ring systems including corrosion inhibition (6-8), antimicrobial activity (8,9), fuel oil additives (6,10) and insecticidal activity and insect repellency (11). Several substituted hexahydropyrimidines have exhibited antitumor activity (12-14). Substituted imidazolidines have been used to improve the crease resistance of cotton fabric (15,16).

In the course of attempting to develop a procedure for the preparation of N,N'-dimethylol derivatives of N,N'-diamides of ethylene-diamine for testing as crosslinking agents for cotton fabric, high yields of 1,3-diacyl imidazolidines were inadvertently obtained:



1,3-Diacyl hexahydropyrimidines were obtained when the procedure was carried out employing diamides of 1,3-diamines. Since 1,3-diacyl derivatives of imidazolidine and hexahydropyrimidine have received no significant attention in the literature, a number of compounds in each series were prepared for study.

EXPERIMENTAL PROCEDURES

Materials

All of the materials were of reagent grade and were purchased from commercial sources.

Procedures for Diamides

Method A. N,N'-Ethylenebisoleamide and N,N'-propylenebisoleamide were prepared by adding dropwise with stirring two molar proportions of oleoyl chloride to one molar proportion of the respective diamines in the presence of 2.1 molar proportions of pyridine using benzene as a solvent. After filtration employing a Buchner funnel, the filtrate was washed with dilute hydrochloric acid, followed by water, then was dried over anhydrous sodium sulfate, filtered and stripped. The diamides were recrystallized twice from acetone.

Method B. N,N'-Ethylenebisacetamide, N,N'-ethylenebisbutyramide, N,N'-propylenebisacetamide and N,N'-propylenebisbutyramide were prepared by the procedure described in Method A except that after filtration, the filtrate was discarded and the solid on the filter was dissolved in water, neutralized with dilute NaOH and stripped. Absolute ethyl alcohol was added to the solid mixture, after which the insoluble portion was removed by filtration and then the solvent was removed by stripping. The diamide was recrystallized from methanol and dried in a vacuum desiccator over phosphorus pentoxide.

Method C. The remaining diamides were prepared by the procedure described in Method A except that after filtration the filtrate was discarded and the solid on the filter was placed in a Soxhlet and extracted with hot water to remove the pyridine hydrochloride. The product was recrystallized from ethanol and dried in a vacuum desiccator over phosphorus pentoxide.

IR spectra confirmed the preparation of the diamides and excluded the presence of the monoamide and free acid by showing absorption bands at 3.05μ and 6.45μ (NH), and at 6.10μ (amide carbonyl), and the absence of absorption bands at 2.85μ and 3.02μ (amino group), and at 5.89μ (acid carbonyl).

Procedures for Ring Closure

Method 1. 1,3-Diacetylimidazolidine (I) was prepared from N,N'-ethylenebisacetamide (4 g, 0.028 mole) and formaldehyde solution (36.8%, 4.4 g, 0.053 mole) in acetic acid (25 ml) containing a catalytic amount (0.3 ml) of 37% hydrochloric acid. These materials were placed in a flask and stirred by means of a magnetic stirring bar while the temperature was raised to 50 C and held at this temperature for 2 hr. Then the acetic acid, excess formaldehyde solution and hydrochloric acid were removed by distillation at reduced pressure. The product was recrystallized twice from absolute ethyl alcohol and dried in a vacuum desiccator over phosphorus pentoxide.

This procedure was also followed in the preparation of 1,3-dibutyryl- and 1,3-dipentanoylimidazolidine.

1,3-Diacetylhexahydropyrimidine and 1,3-dibutyrylhexahydropyrimidine were also prepared by the procedure used for I from the respective N,N'-propylenebisamides and formaldehyde solution. However, no further purification was required for these products after removal of the acetic acid, formaldehyde solution and hydrochloric acid at reduced pressure.

Method 2. The remaining 1,3-diacylimidazolidines were prepared by the procedure described for I except that after the heating period cold water was added to precipitate the product. The precipitated product was removed by filtra-

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TABLE I

Elemental Analyses and Properties of 1,3-Diacyl Derivatives of Imidazolidine and Hexahydropyrimidine

Compound	Yield, %	Density 30 C	N^{30} D	mp C[a]	% C		% H		% N	
					Exp.	Theory	Exp.	Theory	Exp.	Theory
1,3-Diacetylimidazolidine	80			90-92	53.73	53.83	7.77	7.75	17.91	17.94
1,3-Dibutyrylimdazolidine	78			84-86	62.35	62.23	9.77	9.50	13.10	13.20
1,3-Dipentanoylimidazolidine	90			89-91	65.61	64.95	10.13	10.06	11.75	11.66
1,3-Dihexanoylimidazolidine	90			91-93	67.25	67.13	10.54	10.52	10.47	10.44
1,3-Diheptanoylimidazolidine	90			92-94	69.33	68.87	10.97	10.88	9.38	9.45
1,3-Dioctanoylimidazolidine	90			93-95	70.14	70.31	11.25	11.18	8.63	8.63
1,3-Dinonanoylimidazolidine	90			97-99	71.92	71.55	11.55	11.44	7.73	7.94
1,3-Didecanoylimidazolidine	90			100-102	72.52	72.59	11.67	11.65	7.25	7.36
1,3-Dipalmitoylimidazolidine	89			108-110	76.85	76.30	12.50	12.44	5.04	5.09
1,3-Distearoylimidazolidine	90			108-110	77.85	77.41	12.79	12.66	4.75	4.63
1,3-Dioleoylimidazolidine	90			50-52	77.43	77.87	12.01	12.41	4.66	4.66
1,3-Dipalmitoyl-4-methylimidazolidine	90			58-60	77.34	76.80	12.93	12.53	5.15	4.98
1,3-Diacetylhexahydropyrimidine	b	1.1378	1.4911		56.21	56.48	8.44	8.35	16.44	16.47
1,3-Dibutyrylhexahydropyrimidine	b	1.0454	1.4847		63.66	63.71	9.93	9.80	12.47	12.38
1,3-Dipentanoylhexahydropyrimidine	90	1.0244	1.4814		65.50	66.11	10.31	10.31	10.81	11.02
1,3-Dihexanoylhexahydropyrimidine	94	0.9779	1.4797		67.92	68.06	10.77	10.71	9.96	9.92
1,3-Diheptanoylhexahydropyrimidine	84	0.9843	1.4768		68.88	69.64	10.96	11.04	8.97	9.02
1,3-Dioctanoylhexahydropyrimidine	90	0.9673	1.4774		70.59	70.96	11.35	11.32	8.34	8.28
1,3-Dinonanoylhexahydropyrimidine	92	0.9576	1.4760		71.57	72.08	11.33	11.55	7.72	7.64
1,3-Didecanoylhexahydropyrimidine	90			28-30	73.27	73.06	11.91	11.75	7.14	7.10
1,3-Dipalmitoylhexahydropyrimidine	90			64-66	76.65	76.81	12.58	12.54	4.90	4.98
1,3-Distearoylhexahydropyrimidine	90			66-68	78.05	77.73	13.36	12.72	4.37	4.53
1,3-Dioleoylhexahydropyrimidine	88	0.9183			77.75	77.98	11.95	12.44	4.54	4.55

[a]Uncorrected.
[b]The yield was quantitative.

tion, washed with water, recrystallized twice from absolute ethyl alcohol and dried in a vacuum desiccator over phosphorus pentoxide.

Method 3. 1,3-Dipentanoylhexahydropyrimidine (II) was prepared by the procedure described for I except that after the heating period the mixture was diluted with cold water and extracted with diethyl ether. The extract was washed with water, dried over anhydrous sodium sulfate and stripped under reduced pressure.

The remaining 1,3-diacylhexahydropyrimidines were prepared as described for II except that benzene was used in the extraction instead of diethyl ether.

Densities were determined pycnometrically in a thermostated bath at 30± 0.1 C. The refractive indices were determined at 30 C with a precision Bausch and Lomb refractometer using the D sodium line. The melting points were determined on a Fisher-Johns apparatus and are uncorrected. NMR spectra were determined in deuterochloroform solution with a Varian-A-60-A spectrometer, using tetramethylsilane as an internal reference.

RESULTS AND DISCUSSION

The products obtained from the acid-catalyzed reaction of formaldehyde and N,N'-diamides of ethylenediamine were expected to be N,N'-dimethylol derivatives of the diamides. The compounds isolated, however, did not analyze properly for the dimethylol derivatives and did not show the expected hydroxyl band at 2.9 μ in the IR spectra. The NMR spectra revealed an isolated methylene group in these materials which suggested that cyclization had occurred. Comparison of the product obtained from the reaction of formaldehyde and N,N'-ethylenebisacetamide with an authentic sample of 1,3-diacetylimidazolidine prepared by the reduction of imidazole in acetic anhydride (17) established the presence of the imidazolidine ring in the reaction product. The mixed melting point of the two materials was not depressed, and both gave identical NMR spectra, showing sharp singlets at 4.93 ppm (two hydrogens) and 2.11 ppm (six hydrogens) and a broad singlet at 3.79 ppm (four hydrogens).

The reaction of formaldehyde and N,N'-diamides of 1,3-propylenediamine in acetic acid containing a trace of hydrochloric acid readily yielded 1,3-diacylhexahydropyrimidines. The NMR spectra of these materials showed the isolated methylene group as a sharp singlet at 5.10 ppm. That the reaction is clean-cut and complete is revealed by the fact that two of these compounds, the diacetyl and dibutyryl derivatives, liquids at room temperature, were isolated in quantitative yield after the reaction by removal of solvent and excess formaldehyde and gave suitable elemental analyses without further purification. Their IR and NMR spectra revealed no significant impurities.

The 1,3-diacylimidazolidines and 1,3-diacylhexahydropyrimidines prepared in this work are listed in Table I, along with their physical properties and elemental analyses. Besides, 1,3-diacetylimidazolidine, mentioned above, the only other compound in these two series which appears to be described in the literature is 1,3-dibenzoylhexahydropyrimidine, prepared by reaction of benzoyl chloride with the mixture obtained from the reaction of formaldehyde and 1,3-propylenediamine (18). The method of preparing 1,3-diacylimidazolidines and 1,3-diacylhexahydropyrimidines described in the present work is simpler and more convenient to carry out in the laboratory than either of the procedures (19,20) described in the literature. Attempts to extend this procedure to the preparation of 2-substituted derivatives by condensing acetaldehyde, butyraldehyde, and benzaldehyde with N,N'-ethylenebispalmitamide failed and the diamide was recovered unchanged in each instance. Likewise, attempts to prepare four-membered or seven-membered ring systems by condensing formaldehyde with N,N'-methylenebispalmitamide or N,N'-(1,4-butylene)bispalmitamide by this procedure also failed and the diamides were recovered unchanged.

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