THE REACTION OF DIALKYLMALONYL DICHLORIDES WITH 1,3-DIAMINOPROPANES A NEW ROUTE TO MACROCYCLIC POLYAMIDES AND POLYAMINES

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(Received in USA 30 November 1976; received in UK for publication 12 January 1977)

We wish to report convenient syntheses of the macrocyclic amides, 1 and 2, and their amine reduction products, 3 and 4, by routes that may be applicable to practical synthesis of higher homologs. Unsaturated 1,5,9,13-tetraazacyclohexadecanes, the ring system of 1 and 3, have been widely employed as metal-chelating agents.² The present route offers access to derivatives of a different substitution pattern than those available by synthesis involving β -dicarbonyl derivatives. The current interest in heteroatom-containing macrocyclic systems as chelating and clathrating agents³ accents the need for general and convenient routes to new representatives of these types of substances.



As part of a general program, aimed at synthesis and study of derivatives of 1,5-diazacyclooctanes, we considered routes involving preparation and reduction of their keto derivatives. The 2,6-diketo and 2,4,6,8-tetraketobicyclo derivatives are known, ⁴ and routes from these species appear to offer promise. An alternative involves generation of 2,4-diketo-1,5-diazacyclooctanes,but encounters a serious structural limitation. The 3,3-dialkyl derivatives of this system appear to be subject to a high degree of steric compression, evident in structure 5. In fact, our synthetic routes to 5 have failed to yield a stable, isolable substance of this structure, but instead have generated reasonable yields of 1.



For example, when $\underline{7}$ is treated with dicyclohexylcarbodiimide and l-hydroxybenzotriazole⁵ in dioxane-water at 0.02 <u>M</u> concentration, 50-55 % (nmr yield) of <u>l</u> is obtained, identified mass spectrometrically by its intense molecular ion, 396 m/e. Inspection of models reveals that

 $\begin{array}{c} \begin{array}{c} CH_{3} \\ H_{2} \\ CH_{2} \\ CH_{3} \\ C$

1 may assume conformation 6, which has four characterizing features: 1) the nonbonded interactions are small, 2) the amide functions all can assume the more stable s-trans conformation, 3) the structure is stabilized by transannular hydrogen bonding, and 4) the structure contains regions that are similar in geometry to the β -turn or (4+1 trans) conformational substructure of polypeptides. We conjecture that the stability of this hydrogen-bonded subunit acts as an internal template that facilitates closure to the sixteen-membered ring of 1 over oligomer formation, even under reaction conditions involving high starting material concentrations.



β-turn



portion of conformation

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Cyclic anhydrooligomers of \mathcal{I} of still higher molecular weight may also assume conformations with the above structural features. For example, \mathcal{L} , the anhydrotrimer of \mathcal{I} , may assume conformation \mathcal{B} , with two intramolecular hydrogen bonds. The anhydrotetramer, \mathcal{B} , may be able to assume a conformation with three transannular hydrogen bonds.



Reaction of dimethylmalonyl dichloride with 2,2-dimethyl-1,3-propanediamine is observed to generate 1, 2, and 9, as well as trace amounts of other species that may constitute larger cyclic homologs. Convenient reaction conditions involve addition of acyl halide to amine and three equivalents of triethylamine in acetonitrile at 0°, 0.1 \underline{M} concentration. Yields and properties of products are reported in Table 1. Variation of solvent (benzene or DMF) or reactant concentration (0.1 to 5 x 10⁻⁶ \underline{M}) lead to only a small yield variation(16-33 % of 1).

Substance	Yield		m.p.	nmr peak position	Isolation
	nmr	isolated		(CDC1 ₃) δ	
Ļ	33 %	28 %	246- 251°d.	0.90,1.48,3.05	rapidly soluble hot EtOAc crystals on cooling
2	11	7	222-231°d.	0.84,1.53,2.96	slowly soluble hot EtOAc
<u>9</u>		3	259-260°d.	0.86,1.51,2.96	chromatography,silica gel, 1% acetone-EtOAc
polymer		<u>ca</u> .31		0.83,1.57,2.98 (all broad)	insoluble in acetonitrile

TABLE 1 PROPERTIES OF MACROCYCLIC AMIDES

Similar results are obtained from reactions of dimethyl or diethylmalonyl dichlorides with 1,3-propanediamine, 2,2-dimethyl-1,3-propanediamine, and 2,2-bis(hydroxymethyl)-1,3-propanediamine. Insolubility hinders the isolation and characterization of the less substituted derivatives of 1, derived from 1,3-propanediamine or from malonyl dichloride.

Malonyl diesters are reported to react with 1,4-butanediamine to yield polymers. Reactions of dialkylmalonyl dichlorides with ethylene diamine derivatives have been reported to yield seven- membered cyclic diamides, a surprising result in view of the strain of 3,3-disubstituted

derivatives.

An attempt to establish the presence in 1 of a strong transannular hydrogen bond, by nmr exchange studies in D_2O -DMSO have thus far failed, due to the difficulty of obtaining data of precision sufficient to assign an exchange rate to the fourth of four amide protons. An average exchange half-time of 50 hr is observed (10% D_2O , 25°). Verification of the hydrogen-bonded structures proposed for 1, 2, and 9, as well as the template hypothesis of their formation must await further structural studies and model investigations with n-alkyl derivatives.

Reduction of 1 or 2 with excess diborane in THF (20 hr, reflux), followed by evaporation, acidic hydrolysis, basification, and extraction results in the formation of the tetramine, 3, 75 %, m.p. 154-157°, (M^+ 340 m/e; nmr [CDCl₃] 0.93,2.35 δ)⁷ from 1, or the hexamine,4, 75 %, m.p. 118-120°, (M^+ 510 m/e; nmr [CDCl₃] 0.93,2.40 δ). The formation of 1 from 7 in reasonable yield suggests that proper combinations of fragments may generate 2, 9, or higher homologs by short, simple routes, and this possibility is currently under investigation. The sixteen-membered amide derived from dimethylmalonyl dichloride and 2,2-bis(hydroxymethyl)-1,3-propanediamine is of special interest to us as a precursor for a variety of chelating agents with cage structures. The diborane reduction of this tetramide yields the corresponding tetramine as a crystalline hydrochloride salt in 23 % overall yield, based on the propane diamine, m.p.268°d.

ACKNOWLEDGEMENT

Financial support from the National Science Foundation, Grant CHE 75-07771 and from the Dreyfus foundation is gratefully acknowledged.

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