

The activation parameters for the thermal rearrangement of Ia-d are remarkably close to those found by Mislow and Perlmutter⁴ for the racemization of 2-bromodibenzo [*a,e*]cyclooctatetraene-6,11-dicarboxylic acid (IV) at 120–140°. This similarity in ΔH^* and ΔS^* for the thermal reactions of such similar compounds suggests that the transition states for the rearrangement of I and the racemization of IV may bear a close resemblance. It should be noted that an intermediate of the type III is capable in principle of explaining the racemization as well as the rearrangement.

(4) K. Mislow and H. D. Perlmutter, *J. Am. Chem. Soc.*, **84**, 3591 (1962).

(5) Grateful acknowledgment is made of a grant in support of this work from the Petroleum Research Fund of the American Chemical Society.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF MICHIGAN
ANN ARBOR, MICHIGAN

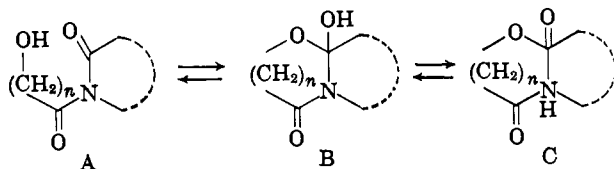
MARTIN STILES⁵
URS BURCKHARDT

RECEIVED JUNE 11, 1964

Amide-Amide Interaction *via* a Cyclol

Sir:

The original proposal by Wrinch¹ that a significant contribution to protein structure might arise *via* cyclols resulting from amide-alcohol, amide-amine, and amide-amide interaction received little support. However, the occurrence of such a structure in the peptide portion of the ergot alkaloids, as established by the synthesis of ergotamine,² and the application of this type of interaction to the synthesis of large-ring depsipeptides³ have stimulated current interest. These syntheses⁴ involved amide-alcohol and amide-ester interactions, both in linear and cyclic systems, as illustrated by the general reaction



We wish to report the first example of a transannular amide-amide reaction, *via* cyclolization, demonstrating the facility of amide-amide interaction in a suitable steric environment.^{5,5a}

1,5-Cyclooctanedione⁶ (m.p. 71–72°) was prepared by cyclization of 2,2-bis(3-cyanopropyl)-1,3-dioxolane⁷ followed by hydrolysis, or more conveniently by ox-

(1) D. Wrinch, *Nature*, **137**, 411 (1936); **138**, 241 (1936); reviewed and summarized: **199**, 564 (1963).

(2) A. Hofmann, A. J. Frey, and H. Ott, *Experientia*, **17**, 206 (1961).

(3) M. M. Shemyakin, Yu. A. Ovchinnikov, V. K. Antonov, A. A. Kiryushkin, V. T. Ivanov, V. I. Shchelokov, and A. M. Shkrob, *Tetrahedron Letters*, No. 1, 47 (1964), and references therein; also reviewed by M. M. Shemyakin at the 3rd International Symposium on Chemistry of Natural Products, Kyoto, Japan, April 15, 1964.

(4) See also R. C. Sheppard, *Experientia*, **19**, 125 (1963).

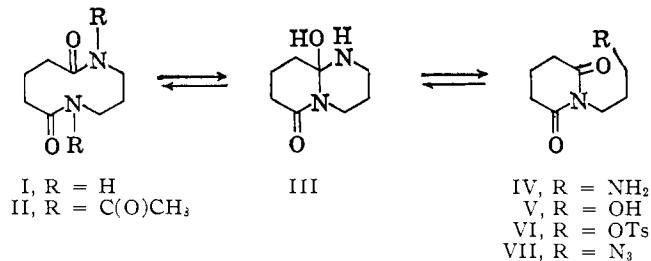
(5) A product which might result from amide-amide interaction has been prepared; however, it was formed from a linear system *via* amide carbonyl- Δ^2 -oxazolinone nitrogen interaction [D. S. Jones, G. W. Kenner, and R. C. Sheppard, *ibid.*, **19**, 126 (1963)].

(5a) NOTE ADDED IN PROOF.—Amide-amide interaction has been invoked to explain, in part, the mass spectral fragmentation pattern of 9- and 11-membered cyclodipeptides [V. K. Antonov, Ts. E. Agadzhanian, T. R. Telesnina, M. M. Shemyakin, G. G. Dvoryantseva, and Yu. N. Sheinker, *Tetrahedron Letters*, No. 13, 727 (1964)].

(6) Satisfactory analyses (combustion and spectral) were obtained for all new compounds; ultraviolet spectra were taken in water, infrared spectra were taken as potassium bromide wafers, and n.m.r. spectra were taken in deuterium oxide.

(7) R. B. Smith, Thesis, University of California, Berkeley; D. Hartley, *J. Chem. Soc.*, 4722 (1962).

dation of 5-hydroxycyclooctanone.⁸ The dioxime ditylosate (m.p. 118–119°), on warming in aqueous dioxane containing potassium bicarbonate, rearranged to 6,10-dioxo-1,5-diazacyclodecane (I, m.p. 233–234°); in the presence of sodium acetate, the acetyl derivative II (m.p. 91–92°) was obtained. Both compounds were purified by crystallization and sublimation and were homogeneous by thin-layer chromatography. Total hydrolysis of the pure compound or the crude reaction mixture in each instance gave only glutaric acid and 1,3-diaminopropane; no γ -aminobutyric acid could be detected. Thus, rearrangement in the present case gave only one of the two isomers usually found with other cyclic diketones.¹⁰



The transannular cyclolization of I to III and ring opening to IV could be followed in 0.1 *N* hydrochloric acid by appearance of an ultraviolet maximum at 208 m μ , which reached a constant value after 2 days at room temperature. Concentration of this acid solution *in vacuo* led to isolation of IV as the hydrochloride (m.p. 194–195°, λ_{\max} 208 m μ (ϵ 14,500)); alkalization of this acid solution with potassium bicarbonate and continuous extraction with methylene chloride led to quantitative recyclization to I. Thus, either form I or IV could be isolated, depending on the pH of the solution; in neutral solution an equilibrium probably exists among I, III, and IV as indicated by the very complex n.m.r. spectrum in deuterium oxide.

The structure of *N*-(3-aminopropyl)glutarimide (IV) was established by synthesis. Glutaric anhydride and 3-aminopropanol gave the *N*-(3-hydroxypropyl)imide (V, m.p. 59–60°, λ_{\max} 211 (ϵ 14,600)) which was converted to amine IV *via* tosylate VI, azide VII, and hydrogenation of the latter. The compound prepared in this manner and isolated as the hydrochloride was identical in all respects with IV isolated from I, and by dissolution in aqueous bicarbonate was converted to I.

In addition to this conclusive evidence for an amide-amide interaction *via* a transannular cyclol, an interesting comparison now can be made between cyclolization *via* amino and hydroxyl groups. Whereas the *N*-(3-aminopropyl)imide IV rapidly forms I in aqueous bicarbonate, the *N*-(3-hydroxypropyl)imide V remains unchanged after several weeks. Clearly,

(8) H. Moell and O. Schlichting, German Patent 1,029,368 (May 8, 1958), assigned to Badische Anilin und Soda-Fabrik. We are indebted to BASF for a sample of this material.

(9) This structure was assigned to material of m.p. 268°, obtained in 1% yield from the reaction of glutaryl chloride and 1,3-diaminopropane [J. Dale and R. Coulon, *J. Chem. Soc.*, 182 (1964)]. See also H. Stetter and J. Marx, *Angew. Chem.*, **69**, 439 (1957), for the preparation of cyclic diamides from diacid chlorides and diamines.

(10) M. Rothe and R. Timler, *Ber.*, **95**, 783 (1962), and references therein to rearrangements with dioximes of cyclohexanedione, cyclodecanedione, and other homologs.

the generalizations¹¹ as to cyclolization of hydroxyacyl lactams may not apply to the amino analogs.

(11) R. G. Griot and A. J. Frey, *Tetrahedron*, **19**, 1661 (1963).

(12) National Institutes of Health Predoctoral Fellow.

(13) This research was supported in part by the U. S. Army Research Office, Durham, N. C.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALIFORNIA
BERKELEY, CALIFORNIA

GEORGE I. GLOVER¹²
HENRY RAPOPORT¹³

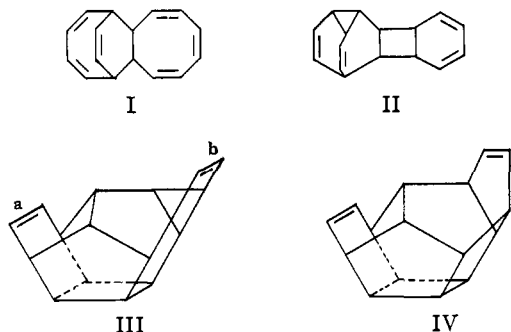
RECEIVED MAY 7, 1964

Dimerization of Cyclooctatetraene. I. Structure of the "Three Double Bond" Dimer

Sir:

The data presented in this communication show that the so-called "three double bond" dimer of cyclooctatetraene actually contains only two double bonds and that the mistaken assignment of the number of double bonds was undoubtedly due to the presence of a cyclopropane ring. Structure III is assigned to the dimer on the basis of the following spectral and chemical data.

Four major dimeric products have been isolated from the thermal dimerization of cyclooctatetraene. Dimerization at temperatures below 100^o1,2 leads to the formation of the two dimers, I and II. Reports indicate that compound I is a precursor to II.^{1,2} At temperatures above 100^o two new products are obtained from the dimerization³⁻⁵; one has two double bonds and was shown to have structure IV by three-dimensional X-ray analysis,⁴ and the other has three double bonds.³ The structures I, II, and IV appear established.^{1,2,4} No definitive evidence has been presented for the structure of the so-called "three double bond" dimer. It absorbs three moles of hydrogen when the dimer is reduced in the presence of a palladium-charcoal catalyst, the third mole being taken up more slowly than the first two.



The dimer was prepared³ as a solid compound melting at 41^o (lit. m.p. 41.5^o).³ The infrared absorption spectrum was identical with that reported by Lord and Walker,⁶ and is in agreement with structure III. Two characteristic absorptions appear in the carbon-carbon double bond region (1615 and 1675 cm.⁻¹). The absorption at 1615 cm.⁻¹ is very similar in position (1606 cm.⁻¹) and intensity to one of the absorptions in the spectrum of the known dimer, IV. The double bond causing the absorption at 1615 cm.⁻¹ is labeled a in structure III. Upon inspection of either III or IV one can see that this double bond (a) is in a bicyclo-

[2.2.2]octene-2 ring system which shows carbon-carbon double bond absorption at 1614 cm.⁻¹ in its infrared absorption spectrum.⁶ The other absorption, at 1675 cm.⁻¹, is remarkably high and must involve the frequency-raising effect of large-angle strain. Such an effect would be expected for structure III since the double bond labeled b is located in a bicyclo[5.1.0]octene-2 ring system, which shows double bond absorption at 1650 cm.⁻¹.⁷ Another feature of the spectrum of the dimer which is in agreement with structure III is the presence of absorption bands characteristic of a cyclopropane ring at 3035, 1035, and 867 cm.⁻¹.⁸

Comparison of the ultraviolet absorption spectra of the dimers III and IV is instructive. The former shows a maximum absorption at 232 m μ (ϵ 2935) and the latter shows only end absorption beyond 224 m μ . Only end absorption would be expected for compound IV since it contains two isolated carbon-carbon double bonds. However, the λ_{\max} at 232 m μ in the spectrum of III is significant. The ability of a cyclopropane ring to enter into conjugation with a neighboring unsaturated system is known,⁹ and Goodman and Eastman¹⁰ have recently shown that the steric relationship between the cyclopropane and the olefin has little consequence spectroscopically. The interaction of a cyclopropane group with an olefin is slightly less than that obtained for conjugated olefins. For example, the conjugated cyclic olefin, 1,3-cycloheptadiene, shows a λ_{\max} at 248 m μ ¹¹ (ϵ 741) while bicyclo[5.1.0]octene-2 shows its λ_{\max} at 237 m μ (ϵ 560).⁷ Thus, the maximum absorption at 232 m μ in the spectrum of III is in good accord with the chromophore comprised of the double bond b and the cyclopropane ring in two bicyclo[5.1.0]octene-2 ring systems.

The complex n.m.r. spectrum of III shows several revealing characteristics. The vinyl proton region shows a complex multiplet (τ 4.2) which corresponds to four protons. For such an observation to indicate more than the presence of two double bonds migration of hydrogen at some stage of the dimerization would be necessary. Such migration seems unlikely in view of the fact that no such rearrangements are necessary to explain the formation of any of the known dimers I, II, and IV, and it will be pointed out later that III is an intermediate in the formation of IV and that II is a very likely precursor to III by an intramolecular Diels-Alder reaction. Another characteristic of the n.m.r. spectrum which is definitive of structure III is the presence of a complex absorption pattern of at least 13 lines corresponding to three protons centered at abnormally high field (τ 9.1). Absorption in this region of the spectrum can be due only to methyl group protons or cyclopropane protons.¹² The possibility of

(7) A. C. Cope, S. Moon, and C. H. Park, *ibid.*, **84**, 4850 (1962).

(8) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1959, p. 29.

(9) For leading references see: M. T. Rogers and J. D. Roberts, *J. Am. Chem. Soc.*, **68**, 843 (1946); R. H. Eastman and S. K. Freeman, *ibid.*, **77**, 6642 (1955); R. S. Mohrbacher and N. H. Cromwell, *ibid.*, **79**, 401 (1957); G. W. Cannon, A. A. Santilli, and P. Shenian, *ibid.*, **81**, 1660 (1959); R. Fuchs, C. A. Kaplan, J. J. Bloomfield, and L. F. Hatch, *J. Org. Chem.*, **27**, 733 (1962).

(10) A. L. Goodman and R. H. Eastman, *J. Am. Chem. Soc.*, **86**, 908 (1964).

(11) E. Pesch and S. L. Friess, *ibid.*, **72**, 5756 (1950).

(12) Methine protons in cyclopropane rings absorb in this region of the spectrum as evidenced by several model compounds. For example, see spectra 273 and 693 in "High Resolution NMR Catalog," Vol. I and II, Varian Associates, Palo Alto, Calif.

(1) G. Schröder, *Angew. Chem. Intern. Ed. Engl.*, **481** (1963).

(2) W. O. Jones, *Chem. Ind. (London)*, **16** (1955).

(3) W. O. Jones, *J. Chem. Soc.*, 2036 (1953).

(4) S. C. Nyburg and J. Hilton, *Acta Cryst.*, **12**, 116 (1959).

(5) W. Reppe, O. Schlichting, K. Klager, and T. Toepel, *Ann.*, **560**, 1 (1948).

(6) R. C. Lord and R. W. Walker, *J. Am. Chem. Soc.*, **76**, 2518 (1954).