[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Cyclic Aminoacyloins and Aminoketones. VIII. N-Cyclopropyl Compounds and Electronic Limitation of Transannular Interaction Between N and C_{CO}[1]

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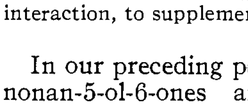
From an infrared spectral analysis of 1-cyclopropyl-1-azacyclononan-5-ol-6-one (II) and 1-cyclopropyl-1-azacycloöctan-5-one (III), it has been found that the electron-withdrawing power of the cyclopropyl group effectively inhibits transannular interaction between N and C_{CO}. Evidence is thus provided for electronic limitation of transannular nitrogen–carbonyl interaction, to supplement the previously demonstrated ring-size, steric strain and environmental limitations.

In our preceding paper on the 1-aryl-1-azacyclononan-5-ol-6-ones and 1-aryl-1-azacycloöctan-5-ones,[2] it was concluded that the apparent diminution in transannular nitrogen–carbonyl interaction  $R{-}\overset{|\delta^+}{\underset{|}{N}}{:}\curvearrowright\overset{|}{\underset{|}{C}}{=}\overset{\curvearrowright}{O}\ \delta^-$, produced by N-phenyl substitution could be accounted for by a combination of steric hindrance and the electron-withdrawing power of the phenyl group. In order to provide information on the possibility of electronic limitation of transannular interaction, it was desirable to select a substituent on nitrogen which would have an electron-withdrawing ability but would not be bulky enough to offer appreciable steric hindrance to N–C_{CO} interaction. The selection had to be limited further by the necessity of this group surviving the rigors of the acyloin and Dieckmann closures of the nine- and eight-membered rings.

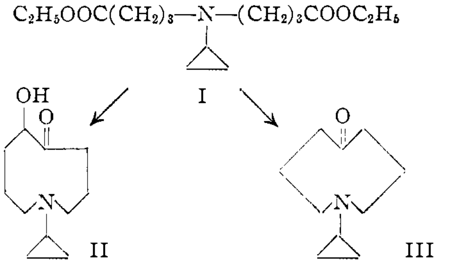
At the outset, the methoxyl group appeared to be a logical choice, since it offers less steric hindrance than a methyl group,[3] and since the lower basicity (pK_a 9.4)[4] of methoxyamine, CH_3ONH_2, compared with that (10.63)[5] of methylamine, indicates that the electron pair on nitrogen should be less available for transannular N–C_{CO} interaction in model methoxyaminoacyloins and methoxyaminoketones than in their methyl analogs. The incorporation of the methoxyl group progressed to the stage of the precursor ester, diethyl γ,γ'-methoxyimino-bis-butyrate, formed by treatment of methoxyamine (O-methylhydroxylamine) with ethyl γ-bromobutyrate, but attempted acyloin and Dieckmann ring closures of this diester failed.

TABLE I

pK_a VALUES (25°)

	Water	50% Ethanol
Methylamine	10.63[5]	
Cyclopropylamine		8.66[6]
Trimethylamine	9.80[5]	
Cyclopropyldimethylamine		7.69[6]
Cyclohexylamine	10.2[7]	9.83[6]

A more fortunate choice of an N-substituent proved to be the cyclopropyl group, which has a strong electron-withdrawing ability, as indicated by the comparative pK_a values in Table I, and meets the requirement of offering a minimum of steric hindrance.[8] Treatment of cyclopropylamine with ethyl γ-iodobutyrate in the presence of potassium carbonate furnished diethyl γ,γ'-cyclopropylimino-bis-butyrate (I), characterized by analysis and infrared maxima indicative of the presence of the cyclopropyl group. This diester was converted by an acyloin condensation under high dilution conditions[2,9] to 1-cyclopropyl-1-azacyclononan-5-ol-6-one (II) and by a Dieckmann ring closure with sodium hydride under high dilution conditions[10] to 1-cyclopropyl-1-azacycloöctan-5-one (III). The cyclopropyl group survived both ring closure methods. The infrared spectrum of the acyloin II as a 3% solution in carbon tetrachloride exhibited a C=O band (center) at 1695 cm.$^{-1}$, or at higher frequency than that observed for the analogous N-methyl (1666), N-ethyl (1671) and N-isopropyl (1691 cm.$^{-1}$) compounds.[11] This is indicative of a lower degree of transannular interaction between N and C_{CO} in the cyclopropyl compound. Moreover, the infrared spectrum of a dilute solution of II in carbon tetrachloride (1.23 × 10^{-2} *M*) had an unsymmetrical band centered on 1694 cm.$^{-1}$, but showed *no* appreciable absorption in the 1671 cm.$^{-1}$ region characteristic of transannular interacted form IV.[12]



Similarly, the infrared carbonyl maximum for the ketone III was found at higher wave number (1691 cm.$^{-1}$ for a 5% solution in carbon tetrachloride) than the maxima for the corresponding N-methyl

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(1) Presented at the Fourteenth National Organic Chemistry Symposium of the American Chemical Society, Lafayette, Ind., on June 14, 1955.

(2) N. J. Leonard and M. Ōki, THIS JOURNAL, **77**, 6241 (1955).

(3) R. Adams and H. C. Yuan, *Chem. Revs.*, **12**, 261 (1933).

(4) Z. Vodrážka, *Chem. Listy*, **46**, 208 (1952); *C. A.*, **46**, 11045 (1952).

(5) D. H. Everett and W. F. K. Wynne-Jones, *Proc. Roy. Soc. (London)*, **A177**, 499 (1941).

(6) J. D. Roberts and V. C. Chambers, THIS JOURNAL, **73**, 5030 (1951).

(7) At 18–20°, see A. Waksmundzki, *Roczniki Chem.*, **18**, 865 (1938); *C. A.*, **33**, 6688 (1939).

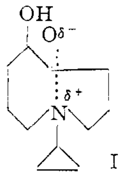
(8) O. Bastiansen and O. Hassel, *Tidsskr. Kjemi, Bergv. Met.*, **6**, 71 (1946); also O. Hassel and H. Viervoll, *Acta Chem. Scand.*, **1**, 149 (1947).

(9) N. J. Leonard, R. C. Fox and M. Ōki, THIS JOURNAL, **76**, 5708 (1954).

(10) N. J. Leonard, M. Ōki and S. Chiavarelli, *ibid.*, **77**, 6234 (1955).

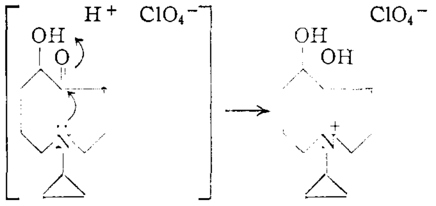
(11) N. J. Leonard and M. Ōki, *ibid.*, **76**, 3463 (1954).

(12) N. J. Leonard, M. Ōki, J. Brader and H. Boaz, *ibid.*, **77**, 6237 (1955).


IV

(1683) and N-cyclohexyl (1687 cm.$^{-1}$) compounds. In dilute solution the band for III appeared at 1695 cm.$^{-1}$ (unsymmetrical), whereas 1-methyl-1-azacyclooöctan-5-one absorbed very weakly at 1695 and strongly at 1681 cm.$^{-1}$.[10] The 1-cyclopropyl-1-azacyclooöctan-5-one thus appears to exist predominantly in the non-interacted form (III). The cyclopropyl group in compounds II and III undoubtedly offers less steric hindrance to transannular N–C$_{\mathrm{CO}}$ interaction than isopropyl or cyclohexyl, so that the limitation of this interaction in the cyclopropyl examples can be ascribed to the electronic effect; *i.e.*, the electron pair on nitrogen is made less available for interaction with the carbonyl.

By the external influence of a protonic acid, however, the interaction can be encouraged (V) to proceed to the formation of a full transannular bond. This is evidenced by the existence of the perchlorate salt of II in the form VI, which shows no C=O absorption. The perchlorate salt of III also exists in the transannular quaternary form, as indicated by its transparency in the 6 μ region. A check is here provided that cyclopropyl does not interfere appreciably sterically with N–C$_{\mathrm{CO}}$ interaction or bonding.


V VI

Experimental[13,14]

Diethyl γ,γ'-Methoxyimino-bis-butyrate.—A mixture of 24.0 g. (0.51 mole) of methoxyamine,[15] 195 g. (1 mole) of ethyl γ-bromobutyrate, 138 g. (1 mole) of potassium carbonate and 600 ml. of ethanol was heated under reflux with stirring for 24 hours. Following cooling, the inorganic material was removed by filtration, the ethanol was evaporated from the filtrate and the residue was taken up in ether. Fractionation gave 25.0 g. (18%) of diester, b.p. 112–115° (0.2 mm.), $n^{20}\mathrm{D}$ 1.4407, selected infrared maxima at 1736 and 1042 cm.$^{-1}$ (liquid film).

Anal. Calcd. for $C_{13}H_{15}NO_5$: C, 56.70; H, 9.15; N, 5.09. Found: C, 56.33; H, 9.37; N, 5.23.

Neither the nine-membered ring methoxyaminoacyloin nor the eight-membered ring methoxyaminoketone could be obtained from this diester by the usual methods.[2]

Diethyl γ,γ'-Cyclopropylimino-bis-butyrate.—This compound was made from cyclopropylamine[16] and ethyl γ-iodobutyrate by the method described above, b.p. 102° (0.06 mm.), $n^{19.5}\mathrm{D}$ 1.4532, yield 87 g. (61%), characteristic infrared maxima at 3070 and 1030 cm.$^{-1}$ (cyclopropyl) and at 1735 cm.$^{-1}$ (ester C=O) (liquid film).

Anal. Calcd. for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54; N, 4.91. Found: C, 63.22; H, 9.36; N, 5.11.

1-Cyclopropyl-1-azacyclononan-5-ol-6-one.—Ring closure of diethyl γ,γ'-cyclopropylimino-bis-butyrate under the usual acyloin conditions[2,9] furnished an unstable, colorless oil, b.p. 74–75° (0.1 mm.), $n^{19.5}\mathrm{D}$ 1.5503, yield 45%, selected infrared maxima at 3450 (O–H), 3070 and 1021 (cyclopropyl), 1695 (C=O), and 1111 cm.$^{-1}$ (C–O) in 3% carbon tetrachloride solution).

Anal. Calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71. Found: C, 67.42; H, 9.76.

The perchlorate was made in ethanol and recrystallized from the same solvent as colorless plates, m.p. 228–229° dec., transparent in the 6μ region, infrared maxima at 3400 and 3250 cm.$^{-1}$ (Nujol mull).

Anal. Calcd. for $C_{11}H_{20}ClNO_6$: C, 44.37; H, 6.77; N, 4.70. Found: C, 43.98; H, 6.61; N, 4.50.

1-Cyclopropyl-1-azacyclooöctan-5-one.—Dieckmann ring closure of diethyl γ,γ'-cyclopropylimino-bis-butyrate was effected under high dilution conditions with sodium hydride[10] and was followed by the usual work-up procedure, giving a colorless, rather unstable oil, b.p. 93–94° (3.0 mm.), $n^{19.5}\mathrm{D}$ 1.4942, yield 42%, selected infrared maxima at 3070 and 1022 (cyclopropyl) and 1691 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.81; H, 10.25. Found: C, 71.98; H, 10.09.

The perchlorate was made in ethanol and recrystallized from ethanol–ether as colorless prisms, m.p. 244–245° dec., transparent in the 6 μ region, infrared maximum at 3340 cm.$^{-1}$ (Nujol mull).

Infrared Absorption Spectra.—These were obtained with a Perkin-Elmer recording spectrophotometer, model 21. For high resolution with the dilute carbon tetrachloride solutions (1.23 ± 0.05 × 10^{-2} *M*), the modifications previously reported[12] were employed.

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[13] All melting points are corrected and boiling points are uncorrected.

[14] We wish to thank Mr. James Brader for determination of the infrared absorption spectra and Mrs. R. Maria Benassi, Mrs. Lucy Chang, Mr. Joseph Nemeth and Mr. R. J. Nesset for the microanalyses.

[15] W. Traube, H. Ohlendorf and H. Zander, *Ber.*, **53**, 1477 (1920).

[16] J. D. Roberts and V. C. Chambers, THIS JOURNAL, **73**, 3176 (1951).